

EXHIBIT 1

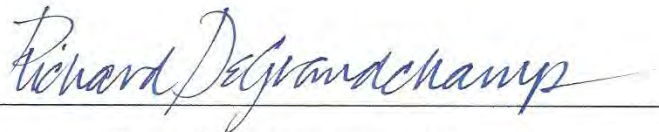
In the United States District Court Eastern District of Washington

City of Spokane v. Monsanto Co.

Expert Report of

Richard L. DeGrandchamp, PhD

October 11, 2019

A handwritten signature in blue ink that reads "Richard DeGrandchamp". The signature is written in a cursive style and is positioned above a horizontal line.

Richard L. DeGrandchamp, PhD

President and Principal Toxicologist

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Richard DeGrandchamp, PhD
Expert Qualifications
October 11, 2019

EXPERT QUALIFICATIONS

I have been practicing toxicology for more than 31 years. I received my BS degree in Biochemistry from Eastern Michigan University and a PhD in toxicology from the University of Michigan, School of Public Health. I received further training as a postdoctoral fellow at the University of Colorado Medical School, Department of Physiology (National Institutes of Health Fellow); Rutgers University School of Pharmacy and Toxicology (Rutgers Fellow); and Cornell University Medical School (Research Associate). I am a member of the Graduate Faculty at the University of Colorado; I have taught for more than 15 years at both the University of Colorado Medical School (Department of Pharmacology) and on the Denver campus (Department of Geography and Environmental Science), where I teach masters candidates, doctoral candidates, and physicians. I am currently the course director for three courses: Environmental Epidemiology, Toxicology, and Risk Assessment. As part of my Risk Assessment and Toxicology courses, I present lectures on the history of toxicology and cancer studies. For the last 4 years, I have committed much of my research to reconstructing the period when the greatest advances in animal cancer testing occurred, from approximately the 1900s to the 1950s. During this effort, I have identified key milestones in cancer research and industrial applied cancer testing. I have reviewed in excess of 150 peer-reviewed publications on topics relating to identifying hallmarks of cancer and the interpretation of pathological lesions caused by carcinogens. I have also reviewed and vetted approximately 600 published studies regarding DDT toxicity, bioaccumulation, and biomagnification and conducted extensive research on the historical development of the oil-water partition coefficient as it relates to lipid solubility. This research forms a significant part of my lectures at the University of Colorado, which I update each semester. In tandem with my research on historical cancer studies in general, I have continued my research on the molecular events triggering PCB-induced cancer, particularly regarding the etiology of non-Hodgkin lymphoma (NHL).

I was also a faculty member at the Naval Civil Engineering Corps Officers School (CECOS), Port Hueneme, California, where I developed the first courses in human health risk assessment, toxicology, and statistical and geochemical analyses for Navy risk assessors/managers and where I developed guidance for remediation of PCB-contaminated Naval bases.

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I am also the President and Principal Toxicologist of Scientia Veritas, L.L.P., a company specializing in toxicology, risk assessment, epidemiology, and geostatistical analyses. I have provided expert support or testimony in Federal Court (retained as an expert for the US Department of Justice) and State Court in toxic tort litigation (concerning polychlorinated biphenyl [PCB]-induced NHL in Plaintiffs) in 10 cases relating to PCB exposures and toxicity. I have authored more than 75 position papers and guidance documents on risk assessment, risk management, statistics, and geostatistics for numerous state and federal governmental departments and regulatory agencies. I have conducted approximately 100 toxicological investigations and risk assessments for PCB-contaminated Superfund and Resource Conservation and Recovery Act (RCRA) sites.

I have authored or reviewed more than 300 human health risk assessments regulated under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; Superfund); RCRA; and Underground Storage Tank (UST) programs; as well as state programs. I have served on numerous scientific review panels and have been a toxicological consultant for the US Environmental Protection Agency (US EPA), Department of the Navy (DON), Department of Energy (DOE), Department of the Air Force, and many state regulatory agencies, as well as chemical, pharmaceutical, and manufacturing companies.

For additional information regarding my qualifications, including publications authored by me within the past 10 years, please see my CV attached to this report as Appendix A.

The following sections present the deposition and trial testimonies I have given in the last four years.

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Deposition Testimonies

2014	<i>Williams et al. v. Monsanto Co, et al.</i> ; Cause No. BC461315 <i>Montgomery et al. v. Monsanto Co. et al.</i> ; Cause No. BC480068 and <i>Hearon et al. v. Monsanto Co, et al.</i> ; Cause No.12SL-CC01497
2015	<i>Helen Briggs et al. v. Freeport-McMoran et al.</i> ; Case No. Civ-13-1157-M <i>Dublin et al. v. Monsanto Co. et al.</i> ; Cause No. 10SL-CC03822-01 <i>Carter et al. v. Monsanto Co. et al.</i> ; Cause No. BC484608 and <i>Dublin et al. v. Monsanto Co. et al.</i> ; Cause No.10SL-CC0322-01
2016	<i>Dauber et al. v. Monsanto Co. et al.</i> ; Cause No. BC483342 <i>Walker et al. v. Monsanto Co. et al.</i> ; Cause No. 1122-CC-9621-01
2018	<i>City of Hartford et al. v. Monsanto Co. et al.</i>
2019	<i>City of San Diego et al. v. Monsanto Co. et al.</i>

Trial Testimonies

06/18–19/2015	<i>Dublin et al. v. Monsanto Co. et al.</i> ; Cause No. 10SL-CC03822-01
09/15–17/2015	<i>Dublin et al. v. Monsanto Co. et al.</i> ; Cause No. 10SL-CC03822-01
03/14/2016	<i>Dauber et al. v. Monsanto Co. et al.</i> ; Cause No. BC483342
04/22/2016	<i>Brownlee et al. v. Monsanto Co. et al.</i> ; Cause No. BC497582
05/13, 16–17/2016	<i>Walker et al. v. Monsanto Co. et al.</i> ; Cause No. 1122-CC-9621-01

Billing Rate

My billing rate is \$250 per hour.

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Summary of Opinions
April 5, 2019

Summary of Opinions

I have been asked to prepare an expert report regarding the history of cancer testing, early-published PCB toxicity studies, and Monsanto's contracted PCB toxicity studies beginning in the early 1930s. I have developed the opinions listed below, as discussed further in Book 1 of my report:

1. Members of the industrial chemical industry had conducted long term, lifetime animal cancer studies when analyzing industrial chemicals like PCBs by the late 1930s.
2. Multiple "triggers" for animal cancer tests applied to PCBs such that animal cancer tests should have been performed well before 1970.
 - a) The molecular structure of PCBs was sufficient to "trigger" cancer tests under industry standards during the 1930s and 1940s because of its benzene-based structure.
 - b) Numerous unique and early hallmarks of cancer in PCB animal studies should have triggered animal cancer studies by as early as 1938 and no later than 1944.
3. Standardized methods for animal cancer testing had been in existence for decades by August of 1970.
4. Monsanto failed to conduct animal cancer tests until the late 1960s/early 1970s.
5. Had PCB animal cancer tests been performed in the 1930s to 1960s, the tests would have shown strong evidence of cancer.

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In addition, I have been asked to evaluate the state of knowledge in the scientific community of bioaccumulation and biomagnification principles during the period when Monsanto manufactured PCBs. I have developed the opinions listed below, as discussed further in Book 2 of my report:

1. At the time Monsanto began manufacturing PCBs, Monsanto must have known that PCBs could bioaccumulate in people and animals.
 - a) Lipid solubility was the sole physicochemical parameter governing the bioaccumulation of highly lipophilic organic industrial compounds into aquatic animals.
 - b) At the time Monsanto began manufacturing PCBs, Monsanto must have known that PCBs were highly lipid soluble.
2. As early as 1945, and by no later than 1950, Monsanto must have known that PCBs would bioaccumulate and biomagnify in humans and animals.
 - a) Between 1945-1950, it was established in the scientific community that DDT bioaccumulated and biomagnified in fat tissue in livestock and animals in the food web.
 - b) PCBs and DDT share the characteristic that caused DDT to bioaccumulate – high lipid solubility.
 - c) As a manufacturer of both DDT and PCBs, Monsanto must have known the chemical characteristics of PCBs and DDT such that Monsanto must have known that PCBs would bioaccumulate and biomagnify in the same manner as DDT in humans and animals.

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I have also been asked to analyze issues relating to the fish consumption advisories applicable to the Spokane River, the risk associated with eating fish in the Spokane River, and the reduction of risk that corresponds with Spokane reducing the amount of PCBs entering the River. I have developed the opinions listed below, as discussed further in Book 3 of my report:

1. The State of Washington has issued Fish Consumption Advisories based on PCBs for the following fish in the following reaches of the Spokane River:
 - Little Falls Pool – Little Falls Dam to Long Lake Dam:
 - Largescale Sucker – Up to 4 meals per month
 - Northern Pikeminnow – Up to 4 meals per month
 - Long Lake (Lake Spokane):
 - Brown Trout – Up to 1 meal per month
 - Common Carp – 0 meals per month
 - Largescale Sucker – Up to 1 meal per month
 - Mountain Whitefish – Up to 2 meals per month
 - Spokane Arm – Mouth upriver to Little Falls Dam
 - Brown Trout – Up to 4 meals per month
 - Largescale Sucker – Up to 1 meal per month
 - Rainbow Trout – Up to 4 meals per month
 - Upriver Dam to Nine Mile Dam
 - Largescale Sucker – Up to 2 meals per month
 - Mountain Whitefish – Up to 1 meal per month
 - Rainbow trout – Up to 2 meals per month

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2. The current fish advisories issued by the WDOH are scientifically tenable and are necessary to protect Washington state residents.
3. The ATSDR/WDOH Health Consultation's recommendations, if followed, will reduce the health threat posed by eating PCB-contaminated fish while maximizing the greatest number of fish meals that can be consumed without fear of PCB-induced toxic effects.
4. The risk assessment presented in the latest 2011 WDOH Health Consultation shows that PCBs pose a cumulative lifetime cancer risk of $1.1E-4$ (one-in-ten-thousand). This risk levels far exceeds the *de minimis* acceptable risk level by 100-fold and to reach acceptable risk levels the fish tissue levels must be reduced by 100-fold.
5. Studies have shown that the groups of people most at risk from eating PCB-contaminated Spokane River fish are from low-income environments.
6. While PCBs were banned decades ago they are still detected in most American bodies today and the highest PCB body burdens in the general public have been shown to be those that eat a diet rich in fish tissue. Sport fishermen have been shown to have body burdens 2-3 times the levels of non-fish eating people.
7. Spokane has taken action to prevent PCB loading to the Spokane river to improve water quality, reduce fish PCB-contaminant levels, lower the

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body burden levels in people that eat Spokane fish. This effort will have a significant impact on lowering PCB body burden and the risk of PCB-related cancer and non-cancer disease.

8. From between the 2001-2005 period and 2030, Spokane's remedial activities will have reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 11-17%. This assumes that Spokane performs the future remedial activities discussed in Michael Baker International's expert report.
9. From between 2012 and 2030, Spokane's remedial activities will have reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 5.5-9%. This assumes that Spokane performs the future remedial activities discussed in Michael Baker International's expert report. This represents a significant reduction in PCB body burden over just an 18-year period and Spokane's efforts will have the greatest impact on reducing PCB exposures.
10. From between 2012 and 2018, Spokane's remedial activities reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 1.4-3.1%.

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1. SUMMARY OF OPINIONS

1. Members of the industrial chemical industry had conducted long term, lifetime animal cancer studies when analyzing industrial chemicals like PCBs by the late 1930s.
2. Multiple “triggers” for animal cancer tests applied to PCBs such that animal cancer tests should have been performed well before 1970.
 - a. The molecular structure of PCBs was sufficient to “trigger” cancer tests under industry standards during the 1930s and 1940s because of its benzene-based structure.
 - b. Numerous unique and early hallmarks of cancer in PCB animal studies should have triggered animal cancer studies by as early as 1938 and no later than 1944.
3. Standardized methods for animal cancer testing had been in existence for decades by August of 1970.
4. Monsanto failed to conduct animal cancer tests until the late 1960s/early 1970s.
5. Had PCB animal cancer tests been performed in the 1930s to 1960s, the tests would have shown strong evidence of cancer.

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2. HISTORICAL CANCER STUDIES

Monsanto should have identified PCBs as a potential animal carcinogen by the mid-1940s. I evaluated the evolution of carcinogenicity testing and the historical protocols used to identify chemical carcinogens starting in the early 1930s.

Monsanto did not conduct any chronic animal studies to investigate the potential carcinogenicity of PCBs until 1969. Monsanto could have conducted those same 1969 studies in the mid-1940s. Had Monsanto conducted their chronic animal carcinogenicity testing for PCBs in the mid-1940s they would have concluded PCBs were carcinogenic.

2.1. By the Mid-1940s, Academic, Regulatory, and Industrial Scientists Had Conducted Hundreds of Cancer Studies on Industrial Chemicals like PCBs.

By 1941, more than 696 animal cancer studies had been completed, the majority of which were published (NCI 1941). These animal cancer experiments were compiled and published by the National Cancer Institute (NCI) and are collectively known as *The Hartwell Compendium*.^[1] Many of the chemicals tested for carcinogenicity were chemicals produced or used by industry to manufacture diverse synthetic chemicals. Chemical compounds were tested for carcinogenic potency, and summaries were presented in tables covering approximately 284 pages (included in this group were 153 unpublished studies on 61 compounds that had recently been completed by the NCI) and including more than 2,000 scientific references. Out of the 696 studies reviewed, 116 were identified as positive studies presenting evidence that a compound was carcinogenic in animals.

At about the same time in late the 1940s, toxicologists in the industrial chemical industry were also completing their first long-term animal cancer studies. These companies included (at least) Dow Chemical Company, E. I. du Pont de Nemours and Company, and Bayer A.G.. Although other companies were also likely conducting similar toxicity testing, they did not generally

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release confidential information (such as test results) about their products. This is discussed further below.

Dow Chemical Company and DuPont both completed their first long-term animal cancer studies in 1938.[2], [3] Furthermore, DuPont shared their study with the scientific community by publishing its results in a peer-reviewed scientific journal. Like Monsanto, Dow, DuPont, and Bayer were very large chemical manufacturers producing diverse chemical products. Even Monsanto conducted 2-year chronic animal studies on some of its chemical compounds before 1947. However, Monsanto did not conduct any 2-year chronic animal carcinogenicity for PCBs-- which it produced in massive amounts--until around 1970, 40 years after they started PCB production.

Monsanto failed to perform even the most perfunctory and basic toxicity tests for its Aroclors. Monsanto limited its testing of PCBs to LD50 tests, which are performed to determine the PCB dose that would kill rodents with a single high dose. It carried out these tests in order to calculate a "Median Lethal," which is simply the PCB dose that will kill 50 percent of the animals. With these tests, animals were given a single high dose of PCB and when they died, the scientist simply counted the number of dead rodents in the group and the dose that killed half the animals was calculated. These are *lethality tests and not toxicity tests*. No toxicity information is provided in an LD50 test -- not even the cause of death.

Monsanto did not perform sufficient toxicity testing to understand the risk associated with long-term exposure despite urgent warnings from occupational physicians and industrial hygienists that chemical companies had the responsibility to protect the general public from their toxic products. For example, at the Seventh Annual Meeting of Members of the Industrial Hygiene Foundation of America, Inc. (an association to which Monsanto belonged) in 1942, Dr. Holden gave a presentation titled "What the Foundation Plant Surveys are Disclosing," highlighting that the major chemical companies were testing their products for toxicity and urged all chemical to do so as well:[4]

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Foundation surveys made this year disclose an increased appreciation by management of the application of interpretive and preventive health measures to conditions in the workplace...The Foundation is now engaged in a study of the toxicity of the products of reaction from the manufacture of a new chemical by a member company. During the laboratory stages of the developmental work on this chemical there were no indications of danger. Ten days after it was placed in pilot production to workmen were stricken seriously from exposure to the chemical or one of the byproducts. By means of the data obtained from animal studies it will be possible to avoid a recurrence of this tragic experience. Every new chemical or product should be investigated as to its toxicity before it is prepared in large amounts and released to the public. This practical common-sense procedure is followed by several larger producers of synthetic chemicals. [emphasis added]

Historically, chemical companies were notoriously secretive and forced confidentiality agreements with their scientific/medical staff about toxicity tests on their products.

Consequently, it was rare for companies to provide detailed information to the press or publish the toxicological results of their in-house or contract testing in peer-review journals where other companies could monitor their activities. Recently, more chemical companies are trumpeting their past historical industrial testing successes.

From my research, it is clear that the major chemical companies had invested considerable effort and money into developing testing protocols and implementing them with the goal of protecting their workers and the general public.

It is important to note that chemical companies like Dow and DuPont, just like Monsanto, were under no regulatory requirement or laws mandating performance of cancer tests. Nevertheless, a number of major chemical companies started their cancer testing programs in the late 1930s. It is clear that these companies practiced the “precautionary principal” wherein they tested their products for toxicity and carcinogenicity before they released them into the general public.

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At the same time that Dow and DuPont had incorporated long-term cancer testing protocols for their chemical safety programs, international chemical companies were similarly engaged. For example, Bayer AG was founded between 1881 and 1913 had started “large-scale testing” in the late 1930s. Early on, the company produced dyestuffs. In later years, it added more chemicals and drugs to their product line.

To ensure the safety of its products, Bayer A.G. built a large toxicological testing facility named the “Institute of Experimental Pathology” and began testing their chemicals to identify potential carcinogens in the late 1930s. In 1958, Bayer’s Dr. Hackmann authored a book chapter titled: “Problems of Testing Preparations For Carcinogenic Properties in the Chemical Industry,” in *Ciba Foundation Symposium on Carcinogenesis, Mechanism of Action*, which is the most detailed discussion of the types of animal cancer experiments that were being conducted by industrial toxicologists in the late 1930s.[5] He shared information on the cancer testing protocols they used and the difficulties they faced but overcame to successfully identify chemical carcinogens in their new products. His report exclusively focusses on “applied industrial toxicity testing” and it was performing industrial toxicology tests on a large scale. Despite the scientific challenges and significant costs associated with cancer testing, by the late 1930s¹ Bayer was already committed to conducting “large-scale animal cancer tests” of “all kinds of chemical products” to ensure their safety:

With the growing recognition of chemical causes of cancer, the testing of chemical preparations for carcinogenic activity has become a major problem in industry.

Somewhat more than twenty years ago we started in our Elberfeld research centres [sic] large-scale tests of all kinds of chemical products. By that time fundamental work on chemical carcinogenesis-in which British research workers, as is known, had a large share-had been carried out. [emphasis added]

It is important to note that he specifically recognizes and gives credit to the hundreds of cancer studies that had been published in the 1930s. These are the very same 1930s studies I have

¹ Hackmann noted that Bayer had started their cancer studies more than 20 years before his publication.

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discussed above, and Dr. Hackmann acknowledges that they formed the basis of A.G. Bayer cancer studies.

In discussing how they selected their industrial chemicals for cancer testing, Dr. Hackmann indicates that the *chemical structures* or “*configuration*” (as he refers to the chemical structure) were the initial triggers for screening new chemicals that should undergo chronic animal cancer tests. He stresses this approach was undertaken as a “precautionary measure.” He notes that chemical companies as the “producer of new chemical materials” are “obliged to test” new products. That is, when newly synthesized industrial compounds are structurally similar to compounds that have been proven to be toxic or carcinogen, that information should trigger investigation to determine the toxic or carcinogenic potential of the new compound. That is, the only way to prove or disprove a chemical was a carcinogen was to generate empirical information and data by testing them in animal studies:

The carcinogenic activity or inactivity of a new product cannot be sufficiently explained- or at best it can only be suggested-from the chemical configuration. The producer of new chemical materials, therefore, feels obliged to test these products in this respect in order that precautionary measures [emphasis added] may be instituted. It is, of course, of very great importance to preclude, or at least to reduce as far as possible, any risk to health or economics connected with carcinogenic activity of a product.

Bayer was following a “precautionary” principle, whereby a company carries the burden of ensuring its product is safe before releasing it to the general public. By producing and selling millions of pounds of PCBs without first conducting toxicity and carcinogenicity tests, Monsanto failed to comply with the precautionary principle.

Dr. Hackmann also notes that when new chemicals were developed in the chemical industry it was not always possible to determine how humans would ultimately be exposed. Therefore, it was necessary to consider all routes of exposure in animal cancer testing, and, while this effort could be costly, it could be justified if the new compound was economically important:

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In dealing with new chemical substances it is not always easy to adapt the method of application to their mode of action, which in many cases is not known and can only be guessed at. For new substances important enough to justify the great efforts and expenditure, there is the possibility of employing as many methods of application as possible on several species of animal. With some degree of probability, although not absolute certainty, it should be possible to gain information on the activity of new substances by testing them in the following ways: painting tests on mice; injection or implantation tests on rats; feeding tests on rats and, if aromatic amines are to be investigated, perhaps on dogs.

Dr. Hackmann goes on to list many hurdles Bayer faced in testing their chemicals for carcinogenic properties including differences between species, mode of application of test substances, spontaneous tumors in control animals, and choosing the appropriate doses. Despite these technical challenges, however, they continued long-term animal cancer tests in order to follow the precautionary principle. He concludes that while animal cancer studies are not always straightforward, these limitations should not be used as an excuse for failing to conduct animal cancer tests for all chemical products to which the general public could be exposed:

It is very difficult to decide from the results of animal experiments whether these products [Bayer's chemicals] are hazardous to man or not. For the reasons outlined above we cannot always expect to find definitive and reliable answer, although these may be the cases most urgently requiring a definite answer. In spite of this limitation of the value of animal experiments we deem it desirable to subject all products intended for human use to such animal tests. Negative results in animals do not definitely prove innocuousness for humans. Positive results of animal tests offer no clear-cut indication of the degree of danger to man, but they may be a valuable guide to instituting appropriate precautions in time.

the historical record suggests there are likely a number of cancer tests that were performed by companies but not published. Confidentiality was the rule in the chemical industry, and the published internal studies were the exception. As evidence of this, Monsanto had contracted for

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more than 100 toxicity studies from 1934–1972 that did not undergo peer review and were never published. My historical research indicates that it was common practice for a company to not report all toxicological findings. Even today in the chemical industry, while many hundreds of toxicology studies are conducted by industrial toxicology laboratories, few are peer reviewed and published. The scientific literature suggests that on multiple occasions when triggers called for cancer studies to be performed for a potential carcinogen, chemical companies pressured physicians and scientists not to publish their studies. Dr. Hueper, who was a DuPont physician performing toxicity testing on DuPont products, provided an account of how he was encouraged *not* to present his work on bladder tumors to his colleagues:[2]

When, in 1939, I was invited to present my observations on experimental aromatic amino cancers before the International Congress on Cancer in Atlantic City, I received the following warning from the medical director of a chemical company which had been my former employer [DuPont]: ‘We do not care to have any information read or published relative to the experimental work on bladder tumors, and I trust that you are prepared to stand by your contract.’ The paper was not presented at that occasion. Similar episodes involving intimidation and suppression have been reported during recent years by urologists from France and by epidemiologists from England. There can be little doubt that American urologists should advocate industrial controls and gather and publish accurate information on this subject to correct this deplorable situation.

Many prominent scientists in the 1920s and 1930s were likewise pressured not to share toxicity information generated while employees in the chemical industry. For example, Dr. Drinker, who conducted some of the first published work on PCB toxicity (Drinker, studies was pressured by Radium Corporation attorneys not to publish his study on workers exposed to the toxic radioactive compound radium, who suffered degeneration of the jaw and other health effects.[6]–[8] As noted in Claudia Clark’s *Radium Girls: Women and Industrial Health Reform, 1910–1935*. Ultimately, after Radium Corporation submitted a misleadingly-edited version of Drinker’s toxicity report to the New Jersey Department of Labor, Drinker did finally submit his own report.[6]

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2.2. Multiple Triggers for Animal Cancer Tests Applied to PCBs, and Monsanto Should Have Performed Chronic Animal Testing by the Mid-1940s.

Toxicologists use the term “trigger” to describe evidence that should be sufficient to prompt an entity to conduct toxicity tests to study a given chemical. For example, toxicity tests should be “triggered” for a chemical when it shares a similar chemical structure or physicochemical properties with a chemical known to be toxic and/or carcinogenic. There were multiple triggers for PCBs during the 1935 to mid-1940s calling for additional chronic animal cancer tests to be performed.²

2.2.1. The molecular structure of PCBs was sufficient to “trigger” cancer tests under industry standards during the 1930s and 1940s because of its benzene-based structure.

As early as the 1930s, these triggers were based on the chemical structure of the suspect chemical. If a suspected carcinogen had a chemical structure similar to that of another chemical that had been tested and confirmed to be a carcinogen, then the suspected chemical would become a candidate for testing. A determination of carcinogenicity of the chemical could not be made without actual animal testing, but newly synthesized chemicals—like PCBs—with chemical structures similar to known carcinogens were suspected until proven otherwise. This was the foundation and basis for identifying chemicals as candidates for cancer testing in the 1930s and 1940s in both academic research and industrial toxicology.

The exact structure of a chemical (in three dimensions) confers its inherent toxicity and potency. Knowing this, fairly accurate predictions can be made of the carcinogenic potential of chemicals, particularly those that are newly synthesized compounds in the industry. If two compounds are

² The only means to investigate whether a chemical compound is carcinogenic is to conduct 2-year animal tests also called “lifetime studies” in which the animals are dosed daily with the test chemical. The reason lifetime rodent studies are necessary is because there is a relatively long latency period between when animals are first exposed and cancer develops. For example, while cigarette smoke is a known carcinogenic it takes 40-50 years from the time a person starts smoking until tumors develop.

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structurally similar, they will likely produce similar toxic effects at the molecular level and in the same organ organs, but they may have different cancer potencies. This relationship between structure and toxicological activity is called the structure-activity relationship (SAR). Within the field of toxicology, there are distinct branches of toxicology that focus solely on this fundamental SAR relationship. Using the SAR to predict carcinogenicity of a compound was historically, and continues to be, the most cost-effective means to identify potential carcinogens in the chemical industry.³ Indeed, in the modern chemical industry, significant effort and costs are devoted to SAR analyses of newly synthesized chemicals to determine if they have structural similarities to known carcinogens; if they do, they will not advance in development past this first screening stage. DuPont used this strategy in the early years in the Haskell laboratory to screen for toxic effects, identify potentially toxic chemicals at the very early stages of development, and eliminate them quickly:[9]

More than once, though, Haskell's research discovered a problem where the only protection was not to get into the business in the first place. For example, in testing a promising new fire retardant for textiles, the laboratory found the substance was absorbed through the skin and caused severe liver damage. "The company abandoned that one in a hurry, Zapp said.

In addition to stopping all further development of a newly synthesized compound, DuPont was invested in testing all of its chemicals for safety before exposures could occur. In this regard, George H. Gehrmann, MD, whose recommendation to the Executive Committee led to the establishment of DuPont's Haskell Laboratory (and who was a nationally known pioneer in preventive medicine), stated in his speech at the dedication of the DuPont Haskell Laboratory:[9]

We can see now that much suffering, disease and death can be...avoided if sufficient knowledge of the toxicity of chemical compounds is developed before

³ Even today, predicting toxicity and carcinogenicity for untested compounds is still based on similar screening process based on the structure activity relationship. This analytical process is known as the *Quantitative Structure Activity Relationship*. For example, EPA has developed a stand-alone guidance document: *(Quantitative) Structure Activity Relationship [(Q)SAR] Guidance Document* (available at: <https://www.epa.gov/pesticide-registration/quantitative-structure-activity-relationship-qsar-guidance-document>) for predicting toxicity.

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the process of manufacture is started, and before our workmen have a chance to become poisoned.

One of the earliest SARs was knowing that a compound had a benzene-based structure. Early cancer tests involved exposing animals to coal tars, and from there, individual chemicals were isolated from the coal tars and they were tested as pure compounds. While there were many diverse compounds isolated from coal tars, those that had benzene-like characteristics were likely candidates for testing. That is, the benzene-like structure became the trigger to prompt animal cancer testing.

Coal tars were analyzed in the first chemical carcinogen animal test in 1912 when Drs. Yamagiwa and Itchikawa proved that they could induce skin cancer by simply applying coal tar to rabbits' ears, as described in the 1915 report by Itchikawa and Baum.[10] Consequently, this triggered a major effort by the scientific community and the chemical industry to identify the specific chemical compounds in coal tars that were responsible for triggering cancer. As soon as pure compounds could be isolated from coal tar in the early 1930s, they were tested for cancer.[11], [12] An excellent treatise on describing these heady times for the field of toxicology and cancer research was published in 1942 by Dr. Rhoades (Director of Memorial Hospital, Pathology Department, Cornell University).[13] In discussing the explosion of cancer studies being conducted in the 1930s and the fact that all these studies zeroed in on the structural benzene-based triggers from coal tar constituents, he wrote:

It is desirable, then, at the outset to review briefly our knowledge of the chemical cause of [sic] malignant disease. This requires reference to Percival Pott the surgeon celebrated for his description of Pott's fracture. As you are probably well aware, he also described scrotal cancer in chimney sweeps as a disease of industrial origin, due to contact of chimney soot with the abraded skin of the worker. With the development of the coal tar and chemical industry in the middle and late eighteen hundreds, a mass of clinical information became available by which tar and tar products were established as causative of cancer in man. This clinical supposition was supported by experimental evidence when in 1912 Yamagiwa and Itchikawa produced cancer of the rabbit's ear by the persistent application of gas-works tar. This classic experiment provided in an animal a suitable test object for the carcinogenic effect of chemicals, and led to the

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isolation from tar of pure compounds which were capable of inducing malignant disease of chemicals, and led to the isolation from tar of pure compounds which were capable of inducing malignant disease (Cook and his co-workers).

As explained by Dr. Rhoads, the Yamagiwa study made clear to cancer researchers and industrial toxicologists that animal studies could be conducted to test carcinogens prior to the observation of disease in humans. Before the Yamagiwa study, cancer scientists could only wait decades until a significant amount of workers developed cancer. But the human-carcinogen link was further obscured by the fact that chemical companies were not conducting epidemiologic studies, so the incidence of human cancer would not be detected until the number of workers with tumors was extremely high.[2] After the Yamagiwa study, the chemical industry realized that carcinogenicity could be tested for relatively quickly because chronic animal cancer studies only take 1–2 years versus, as opposed to decades in human populations.

By the early 1930s, the chemical purification of coal tar compounds was largely completed, and the benzene-based chemical constituents were isolated. Benzene-based compounds (or, to use Rhoads' terminology, "benzene rings linked together") were the key targets for cancer testing:[13]

As soon as these investigators had isolated one such substance, they immediately began to create, in the laboratory, many synthetic compounds structurally allied to it. This was done in an attempt to ascertain what peculiarity of chemical structure was responsible for the pathogenic effect. They found that, whereas no absolute rule could be laid down, most of the active substances produced were composed of benzene rings linked together [emphasis added], and whereas some modifications did not seem to impair activity, others, though very slight, removed completely the effectiveness.

In 1938, Dr. Hueper, a pathologist at the DuPont Haskell Laboratory of Industrial Toxicology, published a study finding that azo-dyes and other *structurally similar* chemicals were carcinogenic. That azo-dyes were carcinogenic was of no surprise; according to Hueper, azo-dyes were discovered to be carcinogenic in humans as early as 1895.[2] What was new about his study was that he identified other compounds having similar structures were also carcinogenic.

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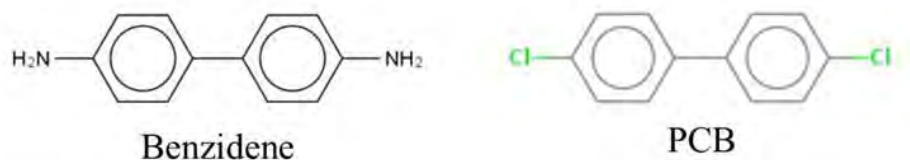
In addition to azo dyes, Hueper studied a number of other chemicals *based on their structural similarity to azo dyes*. In fact, he stated that the use of animal cancer studies enabled him to discover two additional azo dyes that had *not* yet been shown to cause cancer in humans. Thus, the trigger for the new compounds was the *chemical structure* of the known azo dye carcinogen that had already been catalogued.⁴

Further, in discussing his findings from the animal cancer tests he conducted, Hueper concluded that benzidine was a potential carcinogen. He tested benzidine because he identified it as a good candidate for being a carcinogen based on its chemical structure. The relevance of this finding is that benzidine is structurally similar to PCBs (Exhibit 1).

⁴ Compounds that were found to be carcinogenic were cataloged, so when newly synthesized chemicals were produced by industry, they could be compared with the long list of known carcinogens.

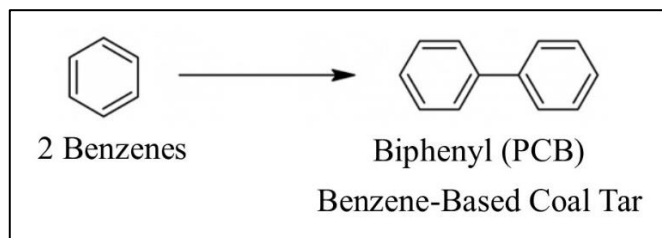
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Exhibit 1. Structural Similarities Between Benzidine and PCB



In addition, the backbone of the PCB molecule is the biphenyl ring, which is a benzene-based compound. Exhibit 2 presents the chemical steps necessary to synthesize the biphenyl ring, in which two benzenes are linked together to make one biphenyl ring structure:

Exhibit 2. Chemical Synthesis of a Biphenyl Ring Structure



Given the structural similarity between benzidine and PCBs, Dr. Hueper's findings would have put a reasonable toxicologist on notice that PCBs should be the subject of animal cancer tests. Of note, Hueper's study was published in the same journal (Journal of Industrial Hygiene and Toxicology) and in the same year as the Bennett et al. study involving PCBs.[14]

As previously discussed, the benzenes that Monsanto used in the first step of making PCBs were actually derived from coal tar. Since coal tars had been known to be carcinogenic, this alone should have been a trigger for testing. However, another trigger that was identified at the time was the isolation of pure *biphenyls* from coal tar. That is, by 1927, biphenyls were shown to be part of the coal tar brew of chemicals. Therefore, it was known by 1927 that coal tar caused cancer and that both benzene and biphenyls were chemicals found in coal tar. This, in itself,

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should have constituted a trigger since PCBs are biphenyl compounds. For example, Marsh and Simpson showed as early as 1927 that diphenyls (a term that is synonymous with *biphenyls*) made up a fraction of coal tars, which they presented in Exhibit 3.[15] As shown below, diphenyls were listed as one of the 11 hydrocarbons that were known constituents and derivatives of coal tar:

**Exhibit 3. Table I from Marsh and Simpson (1927),
Constituents and Derivatives of Coal Tar: Hydrocarbons[15]**

TABLE I	
<i>Constituents and Derivatives of Coal Tar</i>	
HYDROCARBONS	
Serial	
1	Anthracene.
2	Benzene (thiophene free).
3	Cymene.
4	Diphenyl.
5	Fluorene.
6	Mesitylene.
7	Naphthalene.
8	Styrene (dibromide).
9	Toluene.
10	Triphenylmethane.
11	Ortho-xylene.

Through my review and analysis of historical cancer studies, I have observed that the 1930s and 1940s were the most prolific period of cancer testing in the history of toxicology. It should be noted that cancer studies conducted in the 1930s have stood the test of time. The coal tar chemicals identified as carcinogens in the 1930s are still known today as carcinogens.

The most widely used toxicology textbook at both the undergraduate and graduate level is Casarett & Doull's *Toxicology: The Basic Science of Poisons*, by Curtis Klaassen. The textbook includes a chapter on "Chemical Carcinogenicity," within which there is an extensive section on "Organic Chemical Carcinogens," demonstrating the history of cancer testing on coal tars and benzene-based compounds.[16]

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CARCINOGENESIS BY CHEMICALS

By the turn of this century, studies in humans showed that environmental and possibly internal chemical agents are causative factors in the development of cancer (Shimkin, 1977; Lawley, 1944). However, a systematic study of the mechanisms of chemical carcinogenesis was not possible without defined experimental systems. In 1915, the Japanese pathologists Yamagawa and Ichikawa (1915) described the first production of skin tumors in animals by the application of coal tar to the skin. These investigators repeatedly applied crude coal tar to the ears of rabbits for a number of months, finally producing both benign and later malignant epidermal neoplasms. Later studies demonstrated that the skin of mice is also susceptible to the carcinogenic action of such organic tars. During the next 15 years, extensive attempts were made to determine the nature of the material in the crude tars that caused malignancy. In 1932 Kennaway and associates reported the production of carcinogenic tars by means of pyrolysis of organic compounds consisting only of carbon and hydrogen (Kennaway, 1955).

The next section continues:

Organic Chemical Carcinogens

In the early 1930s, several polycyclic aromatic hydrocarbons were isolated from active crude tar fractions. In 1930, the first synthetic carcinogenic polycyclic aromatic hydrocarbon was produced (Miller, 1978). This compound, dibenz-(a,h)anthracene (Fig. 8-1), was demonstrated to be a potent carcinogen after repeated painting on the skin of mice. The isolation from coal tar and the synthesis of benzo(a)pyrene (3,4-benzpyrene) were achieved in 1932. The structures of several polycyclic aromatic hydrocarbons are shown in Fig. 8-1. Polycyclic hydrocarbons vary in their carcinogenic potencies; for example, the compound dibenz (a,c)anthracene has very little carcinogenic activity, while the a,h isomer is carcinogenic (Heidelberger, 1970). The more potent polycyclic aromatic hydrocarbon carcinogens are 3-methylcholanthrene and 7,12-dimethylbenz(a)anthracene. The carcinogenic dibenzo(c,q)carbazole, which has a nitrogen in its central ring, is also considered to be in this class of compounds. Benzo(e)pyrene is reportedly inactive in inducing skin cancer in mice but can “initiate” the carcinogenic process. Perylene is inactive as a chemical carcinogen, whereas chrysene may have slight carcinogenic activity...In 1935,

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Sasaki and Yoshida opened another field of chemical carcinogenesis by demonstrating that feeding of the azo dye, o-aminoazotoluene (3-dimethyl-4-aminoazobenzene) (Fig. 8-2), to rats can result in the development of liver neoplasms. Similarly, Kinoshita (1936) demonstrated that the administration of 4-dimethylaminoazobenzene in the diet also causes neoplasms in the liver. A number of analogs of this compound were prepared and tested for carcinogenic potential.

Note, the chemicals listed in this excerpt are all benzene-based compounds, and this description demonstrates that benzene-based compounds triggered cancer testing in animals in the 1930s.

2.2.2. Numerous unique and early hallmarks of cancer in the animal studies should have triggered animal cancer studies by as early as 1938.

I base this opinion on two highly detailed pathological studies that were published in peer-reviewed scientific journals: Bennett et al. in 1938 and Miller in 1944.[14], [17] In both of these studies, early hallmarks of cancer were reported in both the liver and blood cells (lymphoma). Despite these early reports of the characteristic of the early stages of cancer, it took Monsanto approximately 30 years from the time these cancer hallmarks were first brought to light for Monsanto to perform long-term cancer studies in 1970.

By 1944, the Bennett and Miller studies had reported specific and unique pathological lesions produced by PCBs in the liver. These lesions were early pathological signs of cancer following PCB exposure that were well known by 1938, when the first PCB study was published by Bennett.

By 1944, the following early pathological lesions—seen at the beginning of tumorigenesis—were reported by both Bennett et al. and Miller:

- Hyaline bodies (unique damaged liver cells) which are seen in cancerous liver tissue;
- Evidence of a large number of mitotic figures and areas of hyperplasia (abnormal cell division) of liver cells;
- Bile duct hyperplasia (abnormal cell division of cells lining the bile ducts; can progress to cholangiomas); and

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- Lymphoid hyperplasia follicular lymphoid hyperplasia (abnormal cell division of white blood cells).

I provide a more thorough discussion in Sections 4.2 and 4.3 of the Bennett and Miller studies and the above-referenced indicators.

2.2.3. Studies showing DDT as toxic and a carcinogen should have triggered similar studies for PCBs.

In this section, I extend my historical reconstruction of DDT studies to include toxicity studies that had amassed by 1950. By this time point, scientists had confirmed that DDT was not only toxic but that it was also carcinogenic. These studies were a foreshadowing of the similar PCB toxicity that Monsanto would describe in its own PCB toxicity studies, which it was reluctant to start until 1969. Indeed, the 1945–1950 DDT studies established a pattern of toxic effects that would similarly be described for PCBs in the 1970s. Monsanto, as a manufacturer of both PCBs and DDT,⁵ must have known that DDT and PCBs had similar (but not identical) chemical structures, and should have predicted similar toxicity based on the structure-activity relationships.⁶

Between 1945-1950, a number of well-conducted subchronic and chronic toxicity studies were also being published for DDT, showing toxic effects. In 1946, the FDA's Fitzhugh and Nelson (1946) published a 2-year lifetime animal DDT study that found that DDT was a liver carcinogenic and that tumorigenesis followed a dose-response relationship. Fitzhugh and Nelson explained that a long-term study, rather than a short-term study, was appropriate for DDT since it was lipophilic and bioaccumulative (like PCBs).

Recent studies on the pharmacology of DDT have treated with short-term toxicity experiments on mammals, with its storage in animal tissues, and with its excretion. No

⁵ According to Monsanto's website, it produced DDT from 1944 to 1957.

(<https://monsanto.com/company/media/q/what-is-monsantos-opinion-on-agent-orange-and-ddt/>)

⁶ Monsanto's corporate representative has testified that Monsanto knew the chemical structure of DDT and PCBs when it began making the chemicals. Kaley deposition, *Colella v. Monsanto*, 11/17/2011 (HARTOLDMON0000190-191)

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study of the lifetime effects of DDT on laboratory animals has been reported. Since long-term feeding experiments with other substances in this laboratory have revealed deleterious effects which would not have been seen in experiments conducted for shorter periods of time, it seemed advisable to feed DDT for the lifetime of the rat.

Fitzhugh and Nelson noted that it was the chronic bioaccumulation of small amounts of DDT that were hazardous and caused the toxicity—which is precisely the hazard reported for PCBs in later years. In addition, one of the most outstanding gross pathological changes was increased liver weight; Drinker made this same observation regarding PCBs years earlier, in 1937. Furthermore, Fitzhugh and Nelson’s summary regarding DDT toxicity presents finding similar to those regarding PCBs in that hepatic cell hypertrophy and tumors developed in a dose-response relationship. This study on DDT should have triggered Monsanto to conduct long-term toxicity studies on PCBs in the mid-1940s.

In 1947, Cameron and Burgess published their findings from numerous types of toxicity investigations that began in 1943.[18] In one of the first highly detailed assessments, Cameron and Burgess investigated both acute and repeated exposure to DDT in different pesticide formulations and routes of exposure. These were rather complex experiments that involved gross observations during necropsy, as well as light microscopy pathological examination (primarily liver lesions). They stated:

The introduction of the new synthetic insecticide 2,2-bis (p-chlorophenyl) 1,1,1-trichlorethane (D.D.T.) demands that possible hazards to man be determined and potential dangers safeguarded against. We describe in this paper investigations on the toxicology of D.D.T. which we carried out during the period April, 1943, to March, 1945. These have been the subject of several reports to the Ministries of Production and of Supply, at whose request we have prepared the following account.

Following pathological examination, Cameron and Burgess found that the liver pathology was prominent and noted that similar pathological lesions that were described in PCB studies by Drinker et al. (1937)[19] and Miller (1944).[17]

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In 1948, Fitzhugh once again studied DDT through chronic dosing in rats.[20] And, once again, he stated the importance of conducting chronic studies for highly lipophilic compounds such as DDT because they bioaccumulate with small daily intakes:

Because small amounts of DDT in animal food cause the storage of large amounts in animal products which are used in enormous quantities by man, the question of the safety of DDT on and in food products becomes critically important. Experiments with rats fed DDT over a period of 2 years are discussed.

In this study, Fitzhugh published results from several investigations of chronic dosing in rats, stating that significant liver damage occurs at low exposure levels before any other toxic effects are manifest:

CONCLUSIONS

Significant amounts of DDT are stored in the body tissues of animals, especially in adipose tissues, at levels in the diet as low as 10 p.p.m. Histopathological lesions occur in the livers of rats fed 10 p.p.m. DDT in their diet for 2 years. Individual susceptibility to the toxic effects of DDT varies markedly within any given species. Gross effects such as retardation of growth and hyperexcitability do not occur in animals at the low levels of DDT intake which produce significant liver damage.

In 1950, Laug et al. published a chronic 2-year feeding study in which they exposed animals to DDT levels corresponding to a human dietary level of 5 ppm and found that liver damage occurred even at this low level:[21]

It is interesting to note that hepatic cell alterations are seen in greater degree in the male than in the female. This is in contrast to the observation that at higher levels of intake (800 ppm) the female rat is more, rather than less susceptible to intoxication than the male. The finding of hepatic cell alteration at dietary levels as low as 5 ppm of DDT, has

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and the considerable storage of the chemical at levels that might well occur in some human hepatic cell alterations occur from diets containing as little as 5 ppm.

Laug et al. described pathological lesions similar to those reported by Drinker et al. (1937)[19] and Miller (1944)[17] for PCBs:

Hepatic cell alterations of a type which in our rats have been characteristic for the chlorinated hydrocarbon on group of insecticides in general and DDT in particular, were noted at the 5 ppm and higher levels, but not at 1 ppm... . The changes consisted of hepatic cell enlargement, especially centrolobularly increase in cytoplasmic oxyphilia with sometimes a semihyaline appearance more peripheral location of tile basophilic cytoplasmic granules.

In summary, the studies described show that numerous 2-year chronic feed studies had begun by 1943 and were completed and published by 1946. Monsanto could have followed the same toxicity study designs and methods, simply substituting PCBs for DDT. This should have been done given that PCBs and DDT share key characteristics, such as high lipid solubility. The studies published 1945–1950 should also have been warning signs to Monsanto that PCBs could be equally as toxic and carcinogenic as DDT because the pathological lesions reported in numerous studies for DDT were similar to those previously reported for PCB by both Drinker et al. (1937)[19] and Miller (1944).[17] Therefore, Monsanto should have conducted its 1969 study on long-term exposure to PCBs decades earlier.

If Monsanto had conducted long-term, chronic toxicity tests in the mid-1940s, it would have found that PCBs are bioaccumulative, systemically toxic (liver damage), and carcinogenic in laboratory animals carcinogenic--as it did decades later after finally performing such tests.

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2.3. Robust Toxicological Testing Protocols for Animal Cancer Testing Had Been in Existence since the Mid-1940s

Well-developed and robust toxicity protocols were developed for undertaking carcinogenicity studies by at least the mid-1940s. Accordingly, if Monsanto had followed these methods during this time period, toxicity tests would have shown that PCBs were carcinogenic. They would have produced similar findings of PCB-induced carcinogenesis in the mid-1940s as they found when they finished their first cancer studies in the early 1970s. In fact, standardized testing protocols had been in existence and presented in Hartwell's 1941 compendium of cancer studies. In this document, he discussed the standard features in the design of cancer studies that are still widely used today in academic and industrial laboratories. For example, his review focused on the following features that still must be considered when designing a cancer study:[1]

- Animal species and strain;
- Animal age;
- Animal sex;
- Animal physical condition;
- Purity of tested chemical compound;
- Doses tested;
- Physical state of compound;
- Route of exposure;
- How chemical compounds were administered;
- Number of study animals;
- Survival rate;
- Duration of experiment;
- Rate of tumors formation;
- Number of tumors

In fact, the National Cancer Institute Hartwell compendium (1941) screened out studies thought to be of insufficient quality or in which the studies could be misinterpreted. In this regard, the document does not include mixtures of chemicals or crude grades of chemicals (where low levels of contaminants could confound the interpretation). It also identifies studies where the data is incomplete and or preliminary. Industrial chemical companies were conducting animal cancer testing, and they were using good standard practices, as I have discussed regarding Hueper's DuPont study.[2]

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The protocols that Monsanto finally followed in the early 1970s were similar to those in published literature by the mid-1940s. The vast majority of these early cancer studies cannot be considered slapdash or unreliable. Hartwell (1941) identified the important components of all cancer studies:[1]

It is necessary to have a wide range of information in order to designate a compound as carcinogenic or noncarcinogenic. The carcinogenicity of a substance is known to be influenced by many factors, including the genetic constitution of the animal (species and strain), its age and sex, the diet, the physical condition of the animal, the purity of the chemical compound, the dose, the physical state of the compound, the nature of the solvent or vehicle used in administration, the route or site of application. In addition, the value of the results is dependent on the number of animals used, the survival rate, and the duration of the experiment. Thus, the appearance of tumors is dependent to a high degree on experimental conditions, and both the number of tumors and the rate of their appearance are subject to many modifying influences.

Finally, the following statement by Hartwell could be lifted out of many cancer study protocols being followed today, as there was a concern for both false positive and false negative results:

Furthermore, while failure to obtain tumors in a given case may be attributed to conditions of the experiment and should not always be taken to indicate lack of carcinogenic potency, the reports of tumors obtained should also be subjected to scrutiny and not necessarily accepted as proof of such potency. Many tumors are reported with no histologic support of malignancy; many are also reported as caused by the compound under test when only a few tumors are obtained in animal strains of unknown incidence of spontaneous tumors.

In addition to NCI's Hartwell compendium, many other lengthy lists of animal cancer studies were being compiled during this period, showing that the field of cancer testing had become a very standard practice, even by the late 1930s. The most notable of these include the following:

- A review of the recent literature of tar cancer (1927–1931 inclusive) (Seelig et al. 1933).[22]

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- Chemical compounds as carcinogenic agents. First supplementary report: literature of 1937. (Cook and Kennaway 1938.[11])
- Chemical compounds as carcinogenic agents. Second supplementary report: literature of 1938 and 1939. (Cook and Kennaway 1940.[12])

Based on the sheer number and high quality of peer-reviewed cancer studies that were published in the most prestigious scientific journals of the time, a reasonable toxicologist must have been aware of the potential carcinogenicity of PCBs based on the SAR between PCBs and other industrial compounds that were proven to be carcinogenic by the mid-1940s.

3. PRE-1970 TOXICOLOGICAL STUDIES SHOWED PCBs ARE TOXIC AND CARCINOGENIC

I have reviewed the historical peer-reviewed literature during the early years of Monsanto's PCB manufacturing operations to identify a specific time point when sufficient toxicological information was available to unequivocally show PCBs were extremely toxic and could have cancer-causing properties. My conclusions are based on a detailed review of well over 100 historical peer-reviewed scientific publications starting in the mid-1800s through the mid-1940s.

To create a historical timeline of what scientific information was available to scientists at key points before the mid-1940s. I first identified and confirmed several key early hallmarks of carcinogenicity in which scientist used similar toxicological/pathological nomenclature to describe the early stages of tumorigenesis.[14], [17] This formed the basis for constructing a framework of the state-of-the-science to the mid-1940s so that I could determine if the same pathological terminology was used throughout the mid-1800s through mid-1940s. That is, in my research of cancer studies published in the mid-1800s through the mid-1940s, analyzed whether the description of the early hallmarks of cancer were the same or similar to as those reported in the PCB studies. Based on my review and analysis, I conclude that a competent scientist with knowledge of the cancer studies published in the mid-1800s through the mid-1940s (for other chemical compounds) should have concluded that the pathological lesions described by Bennett

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and Miller (1938 and 1944) for PCBs should have served as a trigger for Monsanto to initiate 2-year chronic animal studies to determine if PCBs were carcinogenic. I have concluded there was sufficient and compelling pathological evidence by that time to serve as a warning to Monsanto that PCBs were carcinogenic in animals. I further conclude that if they had conducted a 2-year animal cancer study at that time, it would have concluded that PCBs were carcinogenic.

It is important to note that while there are likely in excess of 5,000 toxicity studies on PCBs published to-date, it was not necessary for Monsanto to have conducted a lengthy and complex analysis of hundreds of published studies from obscure and dusty scientific journals by 1944 to have triggered a PCB cancer study. A competent toxicologist reviewing just the three following PCB studies published by 1944 would form a conclusion similar to mine; PCBs were toxic and were animal carcinogens:

- **1936:** Dr. Schwartz. Dermatitis from synthetic resins and waxes. American Journal of Public Health. 1936;26:586–592.[23]
- **1938:** Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2):97–123.[14]
- **1944:** Miller JW. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Public Health Reports. 1944;59(33):1085–1093.[17]

Dr. Schwartz's study demonstrates early knowledge of PCBs' toxicity. Further, a competent toxicologist reading just the Bennett et al.[14] and Miller[17] studies would be convinced that there was an urgent need for long-term animal cancer studies.

The hallmarks of early stages of tumorigenesis that were reported in the Bennett et al. and Miller PCB studies and should have been regarded as triggers by Monsanto are as follows:

- The unique formation of hyaline bodies in liver cells, which is early evidence of severe damage in liver cells that is associated with liver cancer:
- Extensive liver cell hyperplasia and mitotic figures (unusual number of liver cell divisions) that is associated with regeneration and cancer.

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- Bile duct hyperplasia (unusual cell division of liver bile duct cells) that is an early hallmark of bile duct cancer.
- Lymphoid hyperplasia, which is an unusual increased number of white blood cells that can lead to lymphomas.
- Pathological lesions and cellular damage were not repaired after PCB exposures was stopped and animals were allowed to recover for 2 months.

This last finding is particularly important to toxicologists. If the pathological changes seen during PCB exposure had recovered—as would be expected—then a competent toxicologist would conclude that the PCB pathological damage would *not* progress to cancer. However, since there was the unexpected finding that the PCB-induced damage in the liver was *not* repaired, it would have been standard practice for any independent and competent toxicologist to follow the progression of the PCB-induced liver damage in order to determine the eventual outcome of the pathological changes.

The eventual outcome of the early hallmarks of cancer reported in 1939 by Bennett and in 1944 by Miller would ultimately be revealed in the 1970s and 1980s by independent scientists conducting 2-year animal cancer studies. In fact, Monsanto's own first 2-year animal studies completed in the early 1970s showed PCB were carcinogenic in animals (despite the fact that these studies included fraudulent data and information). It is my opinion that if Monsanto had conducted that same 1970s chronic cancer study in the 1930s, 1940s, 1950s, and 1960s, it would have concluded that the lesions reported by Bennett et al.[14] and Miller (1944)[17] were indeed early hallmarks of cancer, and at the end of 2 years, Monsanto would have confirmed evidence of PCB-induced cancers.

Further, it is my opinion that any independent competent toxicologist could have predicted by the mid-1940s, that once PCBs were bioaccumulated, they would not be eliminated easily or rapidly. Thus, it was foreseeable by the mid-1940s that PCBs would bioaccumulate in the food web because PCBs possessed the two most important physicochemical properties: lipid solubility and persistence which I discuss in great detail in later.

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3.1. 1936: Dr. Schwartz

Schwartz L. Dermatitis from synthetic resins and waxes. American Journal of Public Health. 1936;26:586–592.[23]

This section presents summary information to support my opinion that an independent competent toxicologist would have known by 1944 that PCBs produce systemic toxicity with the liver being the primary target organ. The toxicological discussion presented by Schwartz (1936) clearly shows that compelling evidence was published before 1944 as he summarized the toxicity as early as 1936.

In 1936, Dr. Louis Schwartz, MD, a Senior Surgeon in the US Public Health Service, published a peer-reviewed study detailing the emerging reports of widespread skin diseases and systemic toxicity among workers who were exposed to chlorinated compounds, including PCBs. While it was widely known that PCBs were causing a specific type of skin disease among PCB workers, Schwartz also reported a case of PCB-related toxicity in the general population—namely, the wife and child of a PCB worker.

The American Journal of Public Health had a wide readership—including industrial hygienists in the chemical industry. It should also be noted that because Schwartz’s study results were previously “read” before the Industrial Hygiene Section of the American Public Health Association at the Sixty-fourth Annual Meeting in Milwaukee, Wisconsin, on October 8, 1935 his findings would likely have been well known throughout the chemical industry.

In stating the purpose of his study, Schwartz noted that while dermatitis associated with manufacture and use of “natural resins” was known, reports of worker dermatitis in the manufacture of “synthetic resins” such as chlorinated naphthalenes and PCBs had not been well studied. However, he warned that exposures were increasing due to a greater number of uses of these compounds in applications such as electric insulators, condensers, insulators on electric wires, paints, varnishes, and lacquers. Obviously, the addition of chlorinated naphthalenes and PCBs to “paints, varnishes, and lacquers” could expose the general public to PCBs. Schwartz

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presents an informed and detailed discussion of how PCBs were synthesized, and he identified specific production steps in Monsanto's PCB manufacturing process that posed the greatest health risks from exposure. In his opinion, distillers refining Aroclors were particularly at risk:

The workers engaged in chlorinating the diphenyl, especially that part of the operation where the crude Arachlor [sic] is being re-distilled to remove impurities, are affected with an acne-like condition of the skin.

The severity of these dermal lesions is described by Schwartz's firsthand accounts of his medical examinations:

The fumes of these compounds cause acne on the face and neck and may penetrate the clothes and cause acne like lesions to develop on the covered parts, the shoulders, and the belt-liner and even on the penis. The lesions on the skin resemble acne. They begin as small, pale, elevated papules, many having no openings in them. They develop into hard cyst-like elevations, under the skin, some of which go on to suppuration [discharging pus], forming boils. Some of the lesions also occur at the mouth of the follicles and resemble the comedones [skin eruptions] and pustules of acne vulgaris.

Although the first appearance of the skin disease may initially appear similar to adolescent acne, the lesions can increase in severity, leading to medically important infections that need intervention. In addition to chloracne, Schwartz described an increasing number of reports of other medical conditions suffered by the PCB workforce:

Those working with the chlorodiphenyls [PCBs] have complained of digestive disturbances, burning of the eyes, impotence, and hematuria [blood in urine].

At the end of his publication, Schwartz made eight specific recommendations to protect workers in the chlorinated naphthalene and PCB industries. He also recognized that workers' wives and children were also being exposed, and he had examined cases where they developed the same toxic effects and medical symptoms as workers. Indeed, his most detailed recommendation focused on protecting workers' family members as evidence seemed to indicate they were much more sensitive to the toxic effects than was the (primarily adult male) workforce.

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Schwartz's first recommendation shows the seriousness and gravity of his concerns regarding the toxicity of chlorinated hydrocarbons, as he stated that production should be "totally enclosed" to achieve zero exposure:

1. The protection of the workers from the irritating chemicals that compose the resins and waxes from the resins and waxes themselves. To do this, the process should be totally enclosed [emphasis added]. If this is not possible, hoods with suction exhaust should be so placed over open processes that dust and fumes are pulled away from the worker and out of the room.

He made two other recommendations noting (emphasis added) the seriousness of the health threats:

*7. There should be periodic medical examination of workers to detect cases of dermatitis and workers in chlorinated naphthalenes and diphenyls [PCBs] should be periodically examined for symptoms of systemic poisoning...[emphasis added].
8. Laws should be passed making it compulsory for factories where there are skin hazards to adopt these measures [emphasis added].*

The fact that Schwartz recommended workers in the PCB industry be "periodically examined" for *systemic poisoning* emphasizes that, as early as 1935, he recognized organ damage to be a major health threat. Workers do not need to be "periodically examined" for skin disease. Those suffering from PCB-related skin disease would have been obvious and immediately diagnosed. However, the only medical symptom that would have been recognized (without robust blood and urine analyses and liver function tests) as systemic toxicity was jaundice (yellowing of the skin and eyes). However, by the time the worker presents with jaundice, the liver has undergone significant damage. What Schwartz was referring to then is an examination of systemic toxicity or *organ damage* needing medical attention, intervention and treatment (however, there is no antidote or therapeutic treatment for PCB-related toxicity).

Schwartz highlighted a case in which he examined a worker's wife and child who presented with the same symptoms seen in the workplace (in this case, Halowax). He describes this confirmed non-occupational exposure case involving family members as follows:

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I have recently seen the wife and child of a worker who had developed comedones [skin eruptions] and pustules from contact with his work clothes which were saturated with halowax and which he was accustomed to wear at home.

Schwartz did not present additional information about any other medical conditions diagnosed in family members, but chloracne is a sentinel symptom of PCB toxicity that often heralds underlying involvement of the liver. It is unclear whether Schwartz conducted other medical tests or examinations, or whether he followed the medical outcomes of the wife and child. However, these cases seem to have had a great impact on him as a physician, since he prepared the most specific and detailed recommendation intended to protect workers' wives and children from take-home contamination:

4. Two lockers should be furnished to each worker. One for his street clothes and one for his work clothes. The lockers for street clothes and work clothes should be in separate rooms, with the shower baths between the locker rooms. The worker coming to work enters the locker room for the street clothes, takes them off, and puts them in the locker and goes into the locker room where his clothes are kept and dons them. From this room he goes to the workrooms through a connecting door. At the end of his shift, he goes through this door to the work clothes locker room, takes off his work clothes and leaves them on the floor or bench to be washed and then goes to the shower baths and bathes and dries. Then he goes to the street clothes locker room, puts on his clothes and goes out of the door leading to the street. It has been estimated at one plant where such a system was instituted that 6 cents a day per worker will take care of furnishing clean work clothes each day.

These specific and meticulous worker hygiene steps make it clear Schwartz thought that protecting the health of wives and children from PCBs and other chlorinated hydrocarbons was paramount. To suggest such precautionary hygiene practices would seem extraordinary if the toxic effects of PCBs were not, in Dr. Schwartz's opinion, significant.

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3.2. 1938: Dr. Bennett

Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2): 97–123.[14]

One of the three “Drinker studies” (published in 1937, 1938, 1939)

In 1938, Dr. Bennett et al. published the first animal study investigating the toxic effects of chlorinated naphthalenes and PCBs in which a thorough pathological examination was conducted. The pathological findings he reported included obvious visible signs that are seen at the beginning stage of cancer. This report described the early hallmarks of tumorigenesis in the liver and it should have been trigger for Monsanto to conduct 2-year chronic animal testing.

This section summarizes a comparative pathological analysis I conducted based on Bennett’s reported pathological findings. Based on my analysis, by 1938, an independent competent scientist would have known that PCBs produced unique pathological lesions associated with the incipient stages of cancer and would have concluded further investigations were warranted.

Bennett’s study reported the following PCB-related toxicity and the most salient pathological lesions in the liver:

- PCBs caused a severe, painful, and disfiguring skin disease in hundreds of workers exposed to PCBs; at the time, this disease was called chloracne (lesions are called hamartomas).
- PCBs likely contribute to human death caused by liver failure with symptoms of jaundice (accumulation of toxic hemoglobin breakdown products).
- PCBs cause extensive organ damage in the liver, resulting in dramatic pathological increases in liver weight.
- PCBs cause significant hemorrhaging (bleeding) in animal livers.
- PCBs cause liver jaundice in animals, leading to death.

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- PCBs cause a unique formation of hyaline bodies that is evidence of severe damage in liver cells and is also an important hallmark of the early stages of cancer.
- PCBs cause extensive mitotic figures (unusual number of liver cell divisions) that can be indicative of the early stages of cancer.
- PCBs cause bile duct hyperplasia (unusual cell division of liver bile duct cells) that is an early hallmark of cancer and can lead to lesions known as cholangiomas.
- Animal livers with PCB-induced pathological lesions and cellular damage are not repaired 2 months after PCB exposure stops and animals are allowed to recover.

Prior to 1935, as indicated by the Schwartz report,[23] it was well established that workers exposed to PCBs suffered from a disfiguring form of a painful skin disease called chloracne. While this particular link between PCB exposure and chloracne was widely known as early as 1937, systemic toxicity involving liver damage was beginning to appear in workers (although Schwartz noted systemic toxicity, he did not discuss any specific cases).

In 1936, three workers exposed to chlorinated naphthalenes and Monsanto's Aroclors developed severe liver damage while working in the New York Halowax Corporation facility—a condition that ultimately proved fatal. Upon medical presentation, the most obvious symptom was acute jaundice (yellow skin and eyes), and these deaths were the first documented fatal cases associated with exposure to chlorinated compounds. Jaundice was confirmed on autopsy, causing alarm and panic in the chemical industry. These three deaths formed the impetus for Halowax Corporation to seek outside academic consultation to investigate how the chlorinated compounds caused jaundice leading to death.

Although it was obvious the chlorinated compounds were the chemicals causing the three Halowax workers' deaths, the toxic pathological sequelae leading to liver damage were unknown. To investigate the triggering events in the liver and subsequent etiology to explain how these compounds could result in death, Halowax retained the services of Dr. Cecil K. Drinker at Harvard University, School of Public Health, and his colleagues (Drs. Madeleine Field Warren and Granville A. Bennett). Drinker was tasked with elucidating the cellular liver damage and determining how the chlorinated compounds caused such severe cases of jaundice. It

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should be noted that since Drinker was charged with determining exactly how the chlorinated compounds Halowax was using in its operations caused jaundice, he formulated the same chlorinated mixtures that workers were being exposed to inside the Halowax facility. In other words, Drinker and his colleagues followed an *applied toxicology* study design using the actual workplace mixtures, rather than a *research toxicity* study that would have focused on individual pure chlorinated hydrocarbon compound mixtures. Following the completion of its experiments, the Drinker team reported its findings in the following three peer-reviewed published studies (collectively, I refer to these as the *Drinker studies* in this report):

- Drinker CK, Warren MF, Bennett GA. The problem of possible systemic effects from certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1937;19(7):283–311. (Minutes from the 1938 Drinker conference at Harvard University are presented at the end of this report.[19])
- Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2): 97–123.[14]
- Drinker CK. Further observations on the possible systemic toxicity of certain of the chlorinated hydrocarbons with suggestions for permissible concentrations in the air of workrooms. The Journal of Industrial Hygiene and Toxicology. 1939;21(5):155–159.[24]

Drinker also prepared the following private report to Monsanto:

- Drinker CK. Report to the Monsanto Chemical Company. September 15, 1938.[25]

In 1937, Drinker also chaired a one-day conference at the Harvard School of Public Health (herein called the *Drinker Conference*) to present his findings on the “systemic effects” of chlorinated naphthalenes and diphenyls (PCBs). Following his presentation, further discussions were held among other attendees, including representatives from Halowax Corporation, Monsanto Chemical Company, General Electric, the US Public Health Service, state health officials from Massachusetts and Connecticut, and others (meeting minutes included at the end of the 1937 Drinker study).

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I have reviewed the Drinker studies and the conclusions of my analysis is that the PCB-induced toxic damage to the liver observed in Drinker's animal studies was consistent with the autopsy reports cause of death. Its conclusion was that Halowax workers died of acute liver damage. Although the Halowax workers were exposed to a mixture of chlorinated naphthalenes and Aroclors, Drinker's findings revealed for the first time that Aroclors were actually more toxic than chlorinated naphthalenes. It was not possible to attribute specific contributions of the chlorinated compounds in the mixture to the liver damage but Drinker's finding that PCBs were more toxic than the other compounds is important.

3.2.1. Background and Purpose of the Drinker Studies

In the first 1937 Drinker study,[19] the researchers clearly stated that, due to the extensive use of chlorinated compounds, a great deal of scientific work had been published on chloracne skin disease (as was illustrated by the 1936 Schwartz study[23]), but little research had focused on the systemic effects to the liver. Therefore, their primary goal was to uncover, if possible, how PCB produced toxic effects in the liver and ultimately death:

Our investigations have not been concerned with chloracne but with the possibility of systemic effects following ingestion or inhalation of such products.

As mentioned above, the investigators were prompted to open a new area of study following a direct request by Halowax Corporation to investigate how the chlorinated compounds caused liver jaundice resulting in death:

In the spring of 1936, the Halowax Corporation, a division of the Bakelite Corporation, called our attention to three fatal cases of jaundice in workmen using chlorinated naphthalenes and chlorinated diphenyl, and requested that the subject be investigated rapidly and thoroughly as possible.

A synopsis of patient presentation and autopsy findings were provided for each of the three patients and their exposures. It was noted that only Patient 1, who was exposed to a small amount (10%) of PCBs, developed chloracne, which developed in tandem with liver disease (jaundice). However, there was no chloracne reported for either Patients 1 or 2, who were only

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exposed to chlorinated naphthalenes (halowax). This may indicate that the chloracne was only caused by PCBs (not chlorinated naphthalenes).

One other striking difference between the three patients is that only Patient 1, who was exposed to PCBs, suffered from gastrointestinal (GI) tract ailments. No such GI involvement was reported for Patients 2 or 3 (who were only exposed to chlorinated naphthalenes). This seems to confirm the reports by Schwartz, who noted that GI distress was reported with PCB exposures.

Based on the limited medical information provided by Drinker,[19] it appears that Patient 1 (who was exposed to PCBs) exhibited greater systemic organ damage (i.e., skin, GI tract, anemia, and liver) and had more severe symptoms than Patients 2 and 3, who were not exposed to PCBs. In fact, Patient 1 presented with only GI complaints. Only later did he succumb to fatal liver disease.

In brief, summaries of the three patients are as follows:

Patient 1. Male. age 21. The previous medical history of this man was in no way significant except for the fact that he had an attack of jaundice about 6 weeks prior to his fatal illness. Late in December, 1936, he became badly constipated and had much abdominal pain and distention. When admitted to the hospital he was slightly jaundiced and was evidently very ill. He was somewhat anemic and his skin, particularly upon the arms, face, chest and back showed many pustules...at autopsy was found to have a cirrhosis of the liver with acute yellow atrophy superimposed upon it. This man had been exposed to low concentrations of vapors arising from a mixture of tetra and pentachloronaphthalenes together with approximately 10 per cent of a refined chlorinated diphenyl. While both he and others engaged in the same work had chloracne... [emphasis added]

Patient 2. This was a young man who died in February, 1936, after an acute illness characterized by jaundice. He had been exposed to fumes arising from a mixture of penta and hexachloronaphthalenes. There is no record of chloracne [emphasis added]. The patient worked with a large number of other people of whom but one (Patient 3), a close friend, had significant illness.

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Patient 3. Another young man employed with Patient 2. He became jaundiced in March, 1936. and died after an illness of 2 weeks. A careful autopsy resulted in a diagnosis of acute yellow atrophy of the liver. Here again no history could be obtained as to a precipitating cause, and there was no record of preceding attacks of jaundice.

Although this simple comparison of exposure to different chlorinated compounds based on case histories from three patients is not definitive, this comparison does indicate that while chlorinated naphthalenes and PCBs produced similar toxic effects in the liver, PCB toxicity involves more organ systems. This deduction was shared by the President of Halowax, Sanford Brown (patients worked in his Halowax plant), who attended the 1937 Drinker/Harvard Conference and compared the health problems before and after the company started using PCBs together with chlorinated naphthalenes in its manufacturing, stating to the attendees:[14]

That is the problem we have had in this case. It [Halowax's chlorinated naphthalenes] has been on the market for 25 years. Until within the past 4 or 5 years there has never been any intimation that it would cause any systemic effects. Thousands and thousands of workmen have dealt with millions and millions of pounds of certain of these materials, particularly the tri-chloranaphthalenes [sic]. Then we come to the higher stages, combined with chlorinated diphenyl and other products, and suddenly this problem is presented to us [emphasis added].

Drinker also noted that “in addition to these three very recent fatalities, we have learned of four other possible cases, none of them fatal.”[19]

In the above quote, Mr. Brown (Halowax Corp) stated an obvious but important fact that most scientists would identify as an important anomaly that required further investigation. That is, it is unusual (or suspicious) that Halowax never experienced any health problems for 25 years and only started seeing health problems when they started using higher chlorinated diphenyls (when workers died). While this *proves* nothing, it should have been a trigger for Monsanto to conduct a similar study using only PCBs—but it did not. Instead, throughout the following years, Monsanto pointed specifically to the Drinker studies as being corrupted and “uncertain” because mixtures of chlorinated naphthalenes and PCBs were used in those studies (Kelly 1950).[26]

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While this is true, nothing prevented Monsanto from conducting their own toxicity testing in which animals would be exposed *only* PCBs.

In addressing the systemic toxicity of chlorinated naphthalenes and PCBs, Drinker developed an overall study design to evaluate the toxicity workers could suffer while performing workplace activities in different parts of the plant. That is, because Halowax used different formulations in different areas of the plant, he tested mixtures of chlorinated compounds with which workers would be expected to come into contact. The exact formulations he tested comprised an attempt to reproduce in his animal studies the actual worker exposure conditions in the Halowax plant. His intent was clearly stated, “These preparations were selected because of their relative importance in industry.”

This experimental design limits the toxicity information that can be extracted for individual compounds such as PCBs. However, after careful analysis of the types of mixtures Drinker tested and comparing the pathological findings for various mixtures, I can conclude that a reasonable toxicologist studying PCBs would have known the following by 1939, based on the totality of the Drinker studies:

- PCBs and chlorinated naphthalenes both produce severe and widespread liver damage;
- PCBs are more toxic than chlorinated naphthalenes;
- PCBs produce a unique pathological constellation of liver organ damage and cellular pathology that had not been seen before; and
- The liver damage is not repaired after exposure stops and animals are allowed to recover.

Despite these deaths and the possibility that Monsanto’s PCBs could have contributed to the cause of death and liver jaundice, Monsanto conducted no additional credible PCB toxicity testing to determine the chronic toxic effects of PCBs for several decades.

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In the sections below, I have extracted PCB-specific toxicity information from the Bennett (1938) study because it presents the pathological findings in the most detail.[14] As I discussed above, in trying to recreate the workplace exposure for the workers who died, the team reproduced the mixtures of chlorinated naphthalenes and PCBs, and tested these in rat studies. Although Bennett et al. did not use pure Aroclors in their study, it was necessary to apply a relatively straightforward comparative pathological assessment to extract PCB-specific toxic information.

3.2.2. Chlorinated Compounds Tested by Bennett

Comparative pathological toxicity evaluations are routine and generally used in the field of toxicology when animals are doses with mixtures of chemical compounds. For example, most toxicity testing involves dosing animals with chemical compounds that are dissolved in a solvent (called a *vehicle*). Because the solvent itself may contribute some toxic effect, it is necessary to include a *control* group in which the animal is only given the solvent or vehicle (these are called the control animals). At the end of the investigation, animals receiving the compound are compared to the controls. Such comparative pathological examinations are common, especially when there is concern that the vehicle itself may be toxic.

I have conducted my *comparative* pathological analysis based on Bennett's reported pathological findings for the following compounds he tested, which are as follows:

- Compound A: Mixture of tri- and tetrachloranaphthalenes [sic] (chlorine content, 49.4%);
- Compound B: Mixture of tetra- and pentachloranaphthalenes [sic] (chlorine content, 56.9%);
- Compound C: Mixture of tetra- and pentachloranaphthalenes [sic], plus chlorinated diphenyl (chlorine content, 43.5%);
- Compound D: Mixture of penta- and hexachloranaphthalenes [sic] (chlorine content, 62.6%);

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- Compound E: Mixture of penta- and hexachloranaphthalenes [sic] (chlorine content, 62.6%);
- Compound F: Mixture of 90% penta- and hexachloranaphthalenes [sic], plus 10% diphenyl (chlorine content, 63%); and
- Compound G: Chlorinated di-phenyl [sic] (chlorine content, 65.0%).

I noted that while Bennett reported that he had used a “pure” Aroclor (Compound G), he later issued an *errata* clarification indicating there was a mix-up with Compound G. While it was reported in the previous studies that Compound G was a “pure” PCB (Aroclor 1265), Drinker’s erratum clarified that the pure PCB tested was not a pure Aroclor, but was a mixture of PCBs and chlorinated diphenyl benzene, stating:

The sixth compound has been listed previously as chlorinated diphenyl [PCBs]. It contained 65% of chlorine and proved very destructive to the liver. Later experiments with compound 13 which contained 68% chlorine [Aroclor 1268] and which was also labelled chlorinated diphenyl, were a surprise to us since this second compound was almost non-toxic. On inquiry it was found that substance 6 was in reality a mixture of chlorinated diphenyl and chlorinated diphenyl benzene and that number 13 was actual chlorinated diphenyl.

To avoid any confusion in my analysis, I have ignored all the experiments and discussions regarding Compound G.

As can be seen in Bennett list of compounds, Compound B and Compound C are very similar; the only difference is that a small amount of PCBs was added to Compound B to make Compound C. In other words, Compound B can be thought of as the vehicle in which Compound C is dissolved (note that the actual amount of PCBs is not presented). With this comparison, it can be determined whether adding a small amount of PCBs either increased, decreased, or had no effect on the toxicity compared with Compound B (the vehicle).

Likewise, a similar comparison can be made between Compounds E and Compound F, since they are identical except for the addition of a small amount of PCBs to Compound E (so it now contains 10% PCBs).

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In summary, the comparisons I made were:

- Toxicity of Compound B (vehicle) versus Compound C (containing PCBs); and
- Toxicity of Compound E (vehicle) versus Compound F (containing 10% PCBs).

For the sake of simplicity, I will herein refer to these comparisons as:

- Compound B versus Compound B+PCBs; and
- Compound E versus Compound E+PCBs.

This study design and comparisons of this type are standard practice in toxicology.

My comparative analysis of PCB-induced liver damage is based on the morphological analysis and pathology lesions described by Bennett for each of the compounds noted above. My analysis focused on four toxicity/pathological endpoints that are most often used to score or rank the severity of compound-induced liver damage.

- Liver weight;
- Liver cell (or hepatocyte) damage;
- Presence, absence, or appearance of hyaline bodies; and
- Mitotic figures.

3.2.3. Compound B versus Compound B+PCBs Feeding Experiments

In comparing the pathological changes representing the relative toxicity of Compound B (pure naphthalenes) and Compound B+PCBs (naphthalenes plus PCBs), I should first note that the experiments for these two compounds were feeding experiments conducted with different concentrations (Compound B+PCBs: 3 g/day; Compound C: 0.5/day). Nevertheless, based on his own experiments, Drinker made a final conclusion that Compound B+PCBs was *twice* as toxic as Compound B (no PCBs). Drinker's conclusion was reported in his later table (Drinker

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1939),[24] in which his recommended safe airborne concentration for Compound B+PCBs was 0.5 mg/cubic meter compared with twice that level for Compound B, which was 1.0 mg/cubic meter. I briefly describe the differences in the pathological damage between Compound B and Compound B+PCBs for the primary pathological lesions in the following sections.

3.2.3.1. *Liver Weight*

Liver weight is a sensitive toxic endpoint that is documented in all toxicity studies on the liver. Increases in liver weight indicate general damage has occurred due to liver toxicity/pathological changes induced by exposure to toxic compounds that target the liver.

The comparative pathology showed that Compound B+PCBs caused significantly more damage than did the vehicle (Compound B). For example, Drinker reported that “there were no significant variations in weights” observed with Compound B. However, for Compound B+PCB, Drinker reported that, “In all animals the livers were enlarged (33 to 90 per cent). The average weight increase was 71 percent.”

3.2.3.2. *Liver Cell Damage*

The liver cell damage resulting from Compound B, was described as follows:

The majority of the liver cells contained large numbers of small fat vacuoles.

Liver cells exposed to Compound B+PCBs appeared to have more extensive and different pathological lesions:

Practically every liver cell was swollen and rounded. Their cytoplasm contained large numbers of hyaline bodies [emphasis added]. These were circular or oval in shape and varied in size from about half the size of a red blood corpuscle to twice the size of the nucleus of a liver cell.

3.2.3.3. *Hyaline Bodies*

While no hyaline bodies were mentioned as being formed with Compound B exposure, there was a stark contrast with animals exposed to Compound B+PCB. These unique structures, which are

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indicative of severe pathology and are potential hallmarks of early cancer, were obvious, numerous, and uniquely arranged only after Compound B+PCB exposure:

In numerous instances, many small hyaline [emphasis added] bodies had fused, forming large circular masses as large or larger than a normal cell. These bodies stained brilliantly with eosin dye. They were often laminated and occasionally contained small clear fat vacuoles in the central portions...The most conspicuous feature of these rats was the presence of large numbers of circular hyaline droplets [emphasis added] in the cytoplasm of the liver cells...Although similar hyaline droplets [emphasis added] were observed in livers of rats exposed to various chlorinated naphthalenes, this type of degeneration occurred much earlier and to a much more marked degree in those rats that were exposed to preparations containing chlorinated diphenyl [emphasis added]... ”

3.2.3.4. Mitotic Figures

Following Compound B exposure, mitotic figures were observed:

Mitotic figures were present in increased numbers indicating accelerated regenerative activity.

Similarly, Compound B+PCBs induced a similar change:

Mitotic figures in liver cells were sufficiently numerous to indicate an increased rate of regeneration.

3.2.4. Compound D versus Compound D+PCBs (10%): Inhalation Exposures

This comparison is based on the pathological changes Drinker reported in which both Compound D and Compound D+PCBs were used in *inhalation experiments* using approximately the same dose and dosing regimen (Compound D: 1.16 mg/per cubic meter for 16 hours/day for 134 days; Compound D+PCB: 1.37 mg/per cubic meter for 16 hours/day for 134 days).

3.2.4.1. Liver Weight

Drinker stated the following for Compound D:

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There were no significant alterations in the liver weights.

However, rats exposed to Compound D with just 10% PCB exhibited liver weight increases of approximately 20%:

There were no very significant alterations in the weights of livers although the majority were slightly swollen (average of 20 percent increase in weight).

3.2.4.2. Liver Cell Damage

There was a distinct difference in the severity of the cellular changes to hepatocytes with the addition of just 10% PCBs. With Compound D, liver cells showed slight damage:

After the initial exposure period of 37 days there was evidence of slight injury to liver cells which appeared more granular than normal.

In contrast, Compound D+PCBs clearly caused increases in liver weight, with hepatocytes that increased in size:

The observed pathological changes consisted of swelling and rounding of liver cells...

3.2.4.3. Hyaline Bodies

The greatest pathological changes between Compound D and Compound D+PCBs were in the hyaline bodies. After exposure to Compound D, the following observations were made:

The cytoplasm of occasional cells contained small acidophilic hyaline droplets [emphasis added] and there was a moderate excess of fat in the form of tiny vacuoles.

In contrast, the following observations were made following exposure to Compound D+PCBs:

The observed pathological changes consisted of swelling and rounding of liver cells accompanied by a definite increase in the prominence of the cytoplasmic granules. Hyaline droplets in the altered cytoplasm were a conspicuous feature. [Emphasis added.]

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3.2.4.4. *Mitotic Figures*

Following exposure to Compound D, there was *no mention* of mitotic figures. In stark contrast, after exposure to Compound D+PCBs, the following statement was made:

Mitotic figures were present in abnormally large numbers.

3.2.5. **Compound D versus Compound D+PCBs (10%): Feeding Exposures**

In addition to the inhalation experiments described above, Drinker also conducted feeding studies of Compound D and Compound D+PCBs using the same dosing regimen (3 g per day) for both compounds. The survival periods for rats at this exposure were approximately one month for both compounds (Compound D: 33 days; Compound D+PCBs: 35 days).

Drinker noted that both groups of animals were ill during this one-month dosing period. However, there was a distinct difference in the severity of the toxic effects between Compound D and Compound D+PCB. The morbidity of rats in the Compound D+PCB was significantly increased (which is surprising, since only a small quantity of PCBs—10%—was added to their food). In fact, the toxic effects of Compound D+PCBs were so severe that imminent death was such a concern that feeding was discontinued after only *12 days*. This was directly due to the morbid state of the rats.

3.2.5.1. *Liver Weight*

Dosing with Compound D resulted in “no significant weight variations.”

In contrast, all the livers weights were increased with Compound D+PCB. Remarkably, the largest liver had more than *doubled* in size:

Macroscopically, the majority of the livers were enlarged, the largest showing an increase in weight of 118 per cent; the average increase was approximately 40 per cent.

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3.2.5.2. Liver Cell Damage

Exposure to Compound D caused some damage to hepatocytes, but these changes were described as follows:

...occurring in cells only occasionally with degeneration occurring rarely.

Macroscopically, “the livers were friable, yellow and mottled” and:

Microscopically they showed marked swelling and vacuolization of the cells. There was also complete degeneration of scattered cells. Occasional mitotic figures were observed (see fig. 4, plate II). Suitable stains revealed very marked fatty degeneration. They contained serous precipitate, a few strands of fibrin, and occasionally a few leucocytes [sic]...Rarely one observed one or two degenerating within these spaces.

Exposure to Compound D+PCBs caused similar lesions, but the damage was much greater than that observed with Compound D, and it appeared to be more widespread throughout the liver. In addition, some pathological lesions that were produced by adding just 10% PCBs were not seen in livers exposed only to chlorinated naphthalenes. The damage that was unique to PCB exposures included obvious pitting and a granular macroscopic appearance of the entire liver. At the cellular level, hemorrhage (bleeding) in the liver, inflammation (involving polymorphonuclear leucocytic invasion), and proliferative bile duct cell division (the finding of this hyperplasia is particularly concerning, as it is associated with cancer).

Macroscopically, “All livers were yellow, friable, and many of them were markedly mottled.... In addition, the external and cut surfaces of the livers appeared slightly pitted or granular.”

Liver cells between such spaces were distorted, swollen, and showed marked fatty degeneration. In these more severely damaged specimens, extensive hemorrhage had occurred (fig. 2, plate VIII)...In many sections the architecture of the liver was so completely altered that it was difficult to recognize the portal areas.

Most notably, bile duct hyperplasia was also described as follows:

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Proliferative changes were occasionally observed in the bile ducts. This was indicated by increased numbers of ducts in certain areas and by mitotic figures in the bile duct epithelial cells. [Emphasis added.]

Drinker also conducted a separate study to investigate the pathological effects associated with a much lower dose for both compounds (0.5 g every second day). While the compounds produced different pathological changes, the overall damage occurred less rapidly and to a lesser degree.

Importantly, however, even with this lower dose, the liver weights of rats treated with Compound D+PCBs increased.

3.2.5.3. *Hyaline Bodies*

Exposure to Compound D produced the following:

Occasional cells contained oval shaped or circular acidophilic hyaline inclusions.

But exposure to compound D+PCBs led to the following observation:

Hyaline droplets in the altered cytoplasm were a conspicuous feature. [Emphasis added.]

3.2.5.4. *Mitotic Figures*

There was a large difference between Compound D and Compound D+PCBs in terms of the emergence of mitotic figures. After exposure to Compound D:

Occasional mitotic figures were observed.

This is much different from what was found after exposure to Compound D+PCBs:

Mitotic figures were present in abnormally large numbers.

In addition to these above differences, a major difference between Compound D and Compound D+PCBs was the observation that just 10% PCBs caused hyperplasia in the bile ducts:

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Proliferative changes were occasionally observed in the bile ducts. This was indicated by increased numbers of ducts in certain areas and by mitotic figures in the bile duct epithelial cells.

3.2.5.5. Summary

In summary, all the above comparisons show that adding a small quantity of PCBs to the chlorinated naphthalenes caused an overall increase in the severity of liver pathology. This should have been an alarming trigger for Monsanto and prompted it to conduct chronic animal studies.

PCB-induced pathology was observed both macroscopically (i.e., by the naked eye) and microscopically. Based on commonly used indices of damage, damage to hepatocytes was also significantly different between the groups.

My conclusion that PCBs produce more severe and unique pathological lesions than do chlorinated naphthalenes is supported by other scientists who have made similar comparisons.

In 1955, Wolfgang Felix von Oettingen, MD, PhD (National Institutes of Health, US Department of Health, Education, and Welfare, Public Health Service) reviewed the same Drinker studies that I have analyzed and presented his assessment of the toxicity and dangers of PCBs in a book entitled, *The Halogenated Hydrocarbons: Toxicity and Potential Dangers*. [27] This is a very lengthy (more than 400 pages) and complete summary of toxicity information that was available at the time of publication. In sections where he specifically discusses the toxicity of chlorinated naphthalenes versus that of PCBs, the main conclusion reached by Dr. von Oettingen was that PCBs are much more toxic than are chlorinated naphthalenes.

As I noted previously, Monsanto had for many years considered the Drinker studies not pertinent to PCBs because pure PCBs were not tested. In later years, Monsanto referred to the studies as confusing when asked about toxicity information (Kelly 1950). [26] However, von Oettingen's conclusions showed that when the Drinker studies were carefully evaluated in a comparative manner, the systemic toxicity produced by PCBs was clear, severe, and long-lasting. Von Oettingen analyzed the Drinker studies in the same detailed comparative manner I did (he did not

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present individual comparisons), but he came to the same conclusion: PCBs are much more toxic than are chlorinated naphthalenes. In so doing, von Oettingen concluded that the Drinker studies provided sufficient and obvious evidence the health threat and danger posed by PCBs.

In comparing the pathological liver lesions resulting from inhaled mixtures of pure chlorinated naphthalenes and chlorinated naphthalenes+PCBs, von Oettingen stated:[27]

Drinker, Warren, and Bennett (1937) and Bennett, Drinker, and Warren (1938) studied the toxicity of a mixture of penta- and hexachloronaphthalenes, [pure chlorinated naphthalenes] containing 62.6 percent of chlorine, and a mixture of 90 percent penta- and hexachloronaphthalenes plus 10 percent refined chlorinated diphenyl, [pure chlorinated naphthalenes+PCBs] containing 63.0 percent of chlorine.

In line with my opinion, von Oettingen concluded that the liver damage from pure naphthalenes was generally limited to “fatty degeneration and centrolobular necrosis:”

They found that with exposure of rats to an average concentration of 8.88 mg. per m.³ of the mixture of penta- and hexachloronaphthalene [pure chlorinated naphthalenes] ...most of them heavily jaundiced, the livers showing marked fatty degeneration and centrolobular necrosis [emphasis added] of the liver cells.

Von Oettingen contrasted the above description of results following exposure to pure naphthalenes with Drinker’s observations after inhalation of chlorinated naphthalenes plus just a small amount of PCBs (10%) in the following description, which indicates a different and more severe pathology:

With inhalation of the same mixture and a mixture of 90 percent penta- and hexachloronaphthalene with 10 percent ...the microscopic examination after 6 weeks’ exposure showed swelling of the liver cells, excessive granulation, hyaline inclusions, and occasional mitotic figures [emphasis added].

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His overall conclusion is identical to mine:

It is, therefore, evident that the toxicity of chlorinated naphthalenes increases with the degree of chlorination and that the chlorinated diphenyls are especially toxic.

Von Ottingen also reviewed the comparative toxicity between chlorinated naphthalenes and PCBs in the feeding experiments:

Feeding experiments with rats receiving about 0.3 gm. of the mixture of penta- and hexachloronaphthalene illustrated also the toxicity of these compounds. The animals sickened and died gradually, and on autopsy they showed injury of the liver. With mixtures of 90 percent penta- and hexachloronaphthalene and 10 percent chlorinated diphenyl the hepatic lesions were extremely severe [emphasis added], which was also the case with the administration of smaller doses (about 0.05 gm.).

3.2.6. Interpreting Bennett's Findings: Early Indications PCBs Were Carcinogenic

In addition to the *degenerative* pathological lesions, Bennett[14] reported hyperplastic changes (cell division that occurs in cancer) and other features suggesting cancer.

There were three obvious and specific pathological changes reported by Bennett that were known by the time of his publication in 1938 that were hallmarks scientists used to identify the early stages of cancer. These are as follows:

- Bile duct hyperplasia;
- Hyaline bodies (also known as hyaline figures and hyaline inclusions); and
- Mitotic figures.

Although the Drinker studies reported these pathological changes in the livers of rats exposed to PCBs, the studies were stopped well before (at approximately 3.5 months) any well-developed tumors would form (usually not seen before 18 months[28]). However, the appearance of bile

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duct hyperplasia, hyaline bodies, and mitotic figures seen so early after rats were exposed to PCBs should have been alarming because these findings were already known to be the first signs of tumorigenesis (see Section 4.2.5 below).

The Drinker studies showed that the PCB-induced liver damage was very severe and—perhaps more importantly—that the widespread pathological lesions were not repaired even after rats were allowed to recover for two months. This unusual finding by itself should have constituted a red flag to Monsanto’s toxicologists/industrial hygienists and triggered chronic animal studies. Monsanto did not know the outcome of the damage from the Bennett study, nor did it seem to care about the prognosis because they did not start any experiments to address this specific issue until the late 1960s.

Unfortunately, Drinker did not offer a prognosis of the long-lasting liver damage, which was still quite pronounced when he killed the animals for examination, but he was not asked to offer any opinion since his charge from Halowax was to determine the cellular liver changes that resulted in death. In other words, his assignment was a cause of death study, rather than a cancer study.

Had Bennett[14] extended the PCB exposures in his study to be a chronic lifetime study, it is my opinion that he would have followed the gradual progression of the hyperplastic changes and mitotic figures to areas of hyperplasia to neoplastic nodules and, finally, to well-defined tumors. In fact, some PCB-induced nodules and tumors reported in later chronic animal studies have been so large that they would have been obvious and detected even with the naked eye (macroscopic examination). For example, in the photograph below, Norback and Weltman (1985) showed a very conspicuous neoplastic nodule measuring a little less than half a centimeter that is visible on the bottom of the right liver lobe (located in the red rectangular outline) (Exhibit 4).[28] This nodule would be immediately obvious upon removing the liver at necropsy. Any suggestion that Drinker would not have seen evidence of cancer in 1939 because cancer studies were not sophisticated or that standard cancer testing protocols were not available is simply not tenable. When tumors are visible to the naked eye and develop in animals exposed to PCBs in 2-year rodent studies, even the most basic cancer study would have concluded that PCBs were carcinogenic.

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**Exhibit 4. Figure 1 from Norback and Weltman (1985),
PCB-exposed Rat Liver at 23 Months[28]**

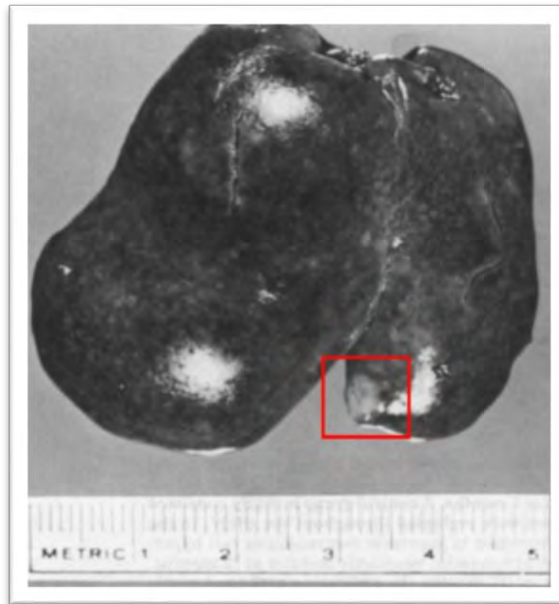


Figure 1. PCB-exposed rat liver; at 23 months. The liver surface is dotted with non-elevated tan foci, .5 to 1 mm in diameter. A neoplastic nodule is present at the tip of one lobe

My opinion that Drinker (or Monsanto) would have found tumors if the study was continued to evaluate lifetime PCB exposures is supported by EPA's analysis of all major cancer PCB studies that were published 1975–1985.[29] In all of these lifetime PCB exposure cancer studies, researchers found a significant statistical increase in the liver tumor incidence rates in lifetime cancer studies. (Note: Although the NCI results were reevaluated and showed fewer tumor rates, Morgan et al. (1931)[30] and Ward (1985)[31] reevaluated the NCI slides for stomach tumors and found 6 adenocarcinomas in 144 exposed rats, which was statistically significant. Furthermore, the tumor rates followed a dose-response relationship (an increase in cancer incidence increased with higher PCB dose levels). The following table from the 1996 EPA report presents the summary results of the tumor incident rates for each study (Exhibit 5).

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**Exhibit 5. Table from EPA (1996)
Liver Tumor Incidences in Rats from Lifetime Exposure Studies,
1975–1985[29]**

Table 2-1. Liver tumor incidences in rats from lifetime exposure studies, 1975–1985			
Study, sex and strain, mixture	Dose	Original ^a	Reevaluation ^{a,b}
Kimbrough et al. (1975) F Sherman, 1260	Control 100 ppm	** 1/173 (1%) 170/184 (92%)	** 1/187 (1%) 138/189 (73%)
NCI (1978) M Fischer, 1254	Control 25 ppm 50 ppm 100 ppm	** 0/24 (0%) 0/24 (0%) 1/24 (4%) 3/24 (12%)	** 0/24 (0%) 1/24 (4%) 1/24 (4%) 3/23 (13%)
NCI (1978) F Fischer, 1254	Control 25 ppm 50 ppm 100 ppm	** 0/23 (0%) 0/24 (0%) 1/22 (5%) 2/24 (8%)	0/23 (0%) 1/24 (4%) 2/24 (8%) 1/24 (4%)
Schaeffer et al. (1984) M Wistar, Clophen A 30	Control ^c 100 ppm	** 2/120 (2%) 42/130 (32%)	8/120 (7%) 16/128 (12%)
Schaeffer et al. (1984) M Wistar, Clophen A 60	Control ^c 100 ppm	** 2/120 (2%) 123/129 (95%)	** 8/120 (7%) 114/125 (91%)
Norback and Weltman (1985) M Sprague-Dawley, 1260	Control 100/50/0 ppm ^d	** 0/32 (0%) 7/46 (15%)	0/31 (0%) 5/40 (12%)
Norback and Weltman (1985) F Sprague-Dawley, 1260	Control 100/50/0 ppm ^d	** 1/49 (2%) 45/47 (96%)	** 1/45 (2%) 41/46 (89%)

^aStatistically significant ($p < 0.05$) by Cochran-Armitage trend test (for experiments with more than one dosed group) or Fisher exact test (for experiments with one dosed group).
^bHepatocellular adenomas or carcinomas
^cDecreases between original and reevaluated denominators are due to lost slides; increases, to slides that were excluded originally but could not be specifically identified for exclusion in the reevaluation.
^dOne control group supported both experiments.
^eDosing was decreased twice during the study.
Source: Adapted from Moore et al. (1994).

Similar results were found in a 1996 lifetime PCB exposure study that examined multiple Aroclors: 1260, 1254, 1242, and 1016 (a refined 1242 Aroclor). The summary results are shown below (EPA 1996) (Exhibit 6). (Note that there was a gender difference between females and males).

**Exhibit 6. Table from EPA (1996),
Liver Tumor Incidences in Rats from 1996 Lifetime Exposure Study[29]**

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Table 2-2. Liver tumor incidences in rats from 1996 lifetime exposure study

Mixture	Dose	Females ^a	Males ^a
Aroclor 1260	Control ^b	** 1/85 (1%)	** 7/98 (7%)
	25 ppm	10/49 (20%)	3/50 (6%)
	50 ppm	11/45 (24%)	6/49 (12%)
	100 ppm	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control ^b	** 1/85 (1%)	7/98 (7%)
	25 ppm	19/45 (42%)	4/48 (8%)
	50 ppm	28/49 (57%)	4/49 (8%)
	100 ppm	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control ^b	** 1/85 (1%)	7/98 (7%)
	50 ppm	11/49 (24%)	1/50 (2%)
	100 ppm	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control ^b	** 1/85 (1%)	7/98 (7%)
	50 ppm	1/48 (2%)	2/48 (4%)
	100 ppm	6/45 (13%)	2/50 (4%)
	200 ppm	5/50 (10%)	4/49 (8%)

**Statistically significant ($p < 0.05$) by Cochran-Armitage trend test.

^aHepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.

^bOne control group supported all experiments.

Source: Adapted from Brunner et al. (1996), Keenan and Stickney (1996)

Collectively, the above studies support my opinion that it is more likely than not that an independent and objective scientist conducting lifetime cancer animal studies in 1938 would have concluded that PCBs were carcinogenic.

My opinion is further supported by the Norback and Weltman study, which was specifically designed to follow the pathological lesions from the first month of exposure to the end of the study 24 months later.[28]. The EPA study summarized those findings:[29]

Norback and Weltman (1985). Groups of male or female Sprague-Dawley rats were fed diets with 0 or 100 ppm Aroclor 1260 for 16 months; the latter dose was reduced to 50 ppm for 8 more months. After 5 additional months on the control diet, the rats were killed and their livers were examined. Partial hepatectomy (a portion of the liver was removed and examined at different periods) was performed on some rats at 1, 3, 6, 9, 12, 15, 18, and 24 months to evaluate sequential morphologic changes. In males and females fed Aroclor 1260, liver foci appeared at 3 months, area lesions at 6 months, neoplastic nodules at 12 months, trabecular carcinomas at 15 months, and adenocarcinomas at 24 months.

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demonstrating progression of liver lesions to carcinomas [emphasis added]. By 29 months, 91 percent of females had liver carcinomas and 95 percent had carcinomas or neoplastic nodules; incidences in males were lower, 4 and 15 percent, respectively (see table 2–1).

In following the progression of the hallmarks of cancer (tumorigenesis), the lesions start as preneoplastic areas (areas of mitotic figures, which were reported in the 1938 Bennett study[14]), progress to nodules, and then progress to carcinomas. This progression is shown in the Norback and Weltman table presented in Exhibit 7.[28]

**Exhibit 7. Table 1 from Norback and Weltman (1985),
Development of Preneoplastic and Neoplastic Hepatocellular Lesions in
Male and Female Rats During Chronic Aroclor 1260 Exposure[28]**

Table 1. Development of preneoplastic and neoplastic hepatocellular lesions in male and female rats during chronic Aroclor 1260 exposure.*																
Lesion	No. of livers with lesions of each three sampled															
	1 mo.		3 mo.		6 mo.		9 mo.		12 mo.		15 mo.		18 mo.		24 mo.	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Focus	0 ²	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Area	0	0	0	0	1	0	2	1	0	3	1	3	0	3	3	2
Neoplastic nodule	0	0	0	0	0	0	0	0	0	1	0	3	0	3	1	3
Trabecular carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	2
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

*These lesions were not present in sequentially sampled control liver.

The photomicrograph in Exhibit 8 from Norback and Weltman shows an example of the early cancer hallmarks at 1 month. This is a liver section containing many mitotic figures (in the red area; they describe this as cell hypertrophy). This the same early pathological evidence of mitotic figures reported by Bennett in 1938, where he stated that “mitotic figures were present in abnormally large numbers.”

**Exhibit 8. Figure 6 from Norback and Weltman (1985),
Hypertrophic Hepatocytes Developed in the Central Lobular Region of the
Liver at 1 Month[28]**

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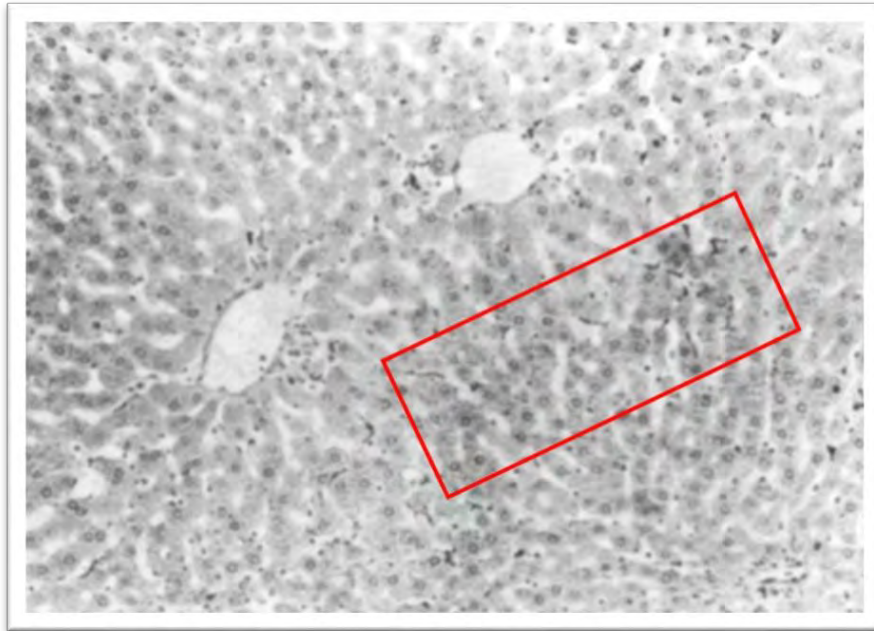


Figure 6. Hypertrophic hepatocytes developed in the central lobular region of the liver obtained at 1 month. H & E; x 160. (Norback and Weltman 1985)

While Bennett's study could not address the issue of cancer because the exposures were insufficiently long, one of his experiments did address the issue of whether the mitotic figures could simply have represented regeneration of damaged cells, indicating repair of the liver.[14] After dosing the rats for approximately 130 days, PCB exposure was discontinued. The livers were then given the opportunity to recover for 2 months (which is normally a sufficient period of time for the liver to show a more normal appearance). The damaged rat livers did *not* recover, which was acknowledged in the following statement regarding for rats exposed to Compounds D and F (90% Compound D with 10% Compound F):

These lesions were still demonstrable after a 2 month's recovery period.

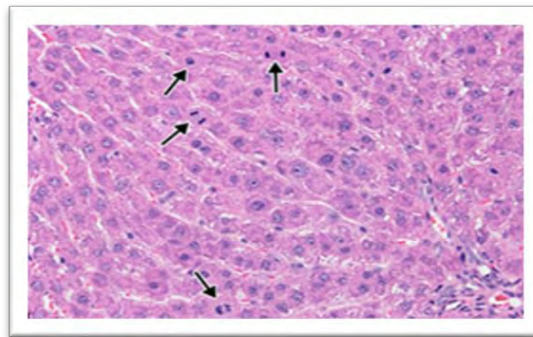
This suggests the tumorigenic progression was not halted.

However, Bennett did observe that cells were rapidly dividing, undergoing extensive cell division. He stated, "mitotic figures were present in abnormally large numbers," which is clear

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evidence of hyperplasia, a well-established prerequisite step in tumorigenesis since the basic definition of cancer is uncontrolled cell division. Tumors develop from these hyperplastic cells that are rapidly undergoing rapid mitotic cell division. Cells that are seen at the light microscope level undergoing cell division are dividing in a process known as mitosis (i.e., it is the chromosomes that are made visible with stains under the light microscope). These mitotic cell divisions are called *mitotic figures*. As shown in the photomicrograph of a liver section below, they are easily identified. (Exhibit 9; National Toxicology Program [NTP].[32])

**Exhibit 9. National Toxicology Program
Photomicrograph of Mitotic Figures in a Liver Section[32]**



Note: Four arrows point to mitotic figures

Source: <https://ntp.niehs.nih.gov/nnl/hepatobiliary/liver/hinmitos/index.htm>

During organ growth (organogenesis) in early development, mitotic figures are numerous as the cells need to multiply for the organ to grow in size. However, once an organ such as the liver reaches its functioning mature size, the cells no longer divide, except in response to injury or cancer. As stated by the NTP, mitotic figures are rare, except in certain conditions.[32]

A high mitotic frequency can be seen during phases of early growth, during physiologic conditions such as pregnancy, or in rodents bearing tumors at other sites. While occasional mitoses can be seen in a normal liver, finding more than one or two mitoses per 10 high-power fields is not typical for adult rodents. In this example [photomicrograph shown above], the high frequency of mitosis

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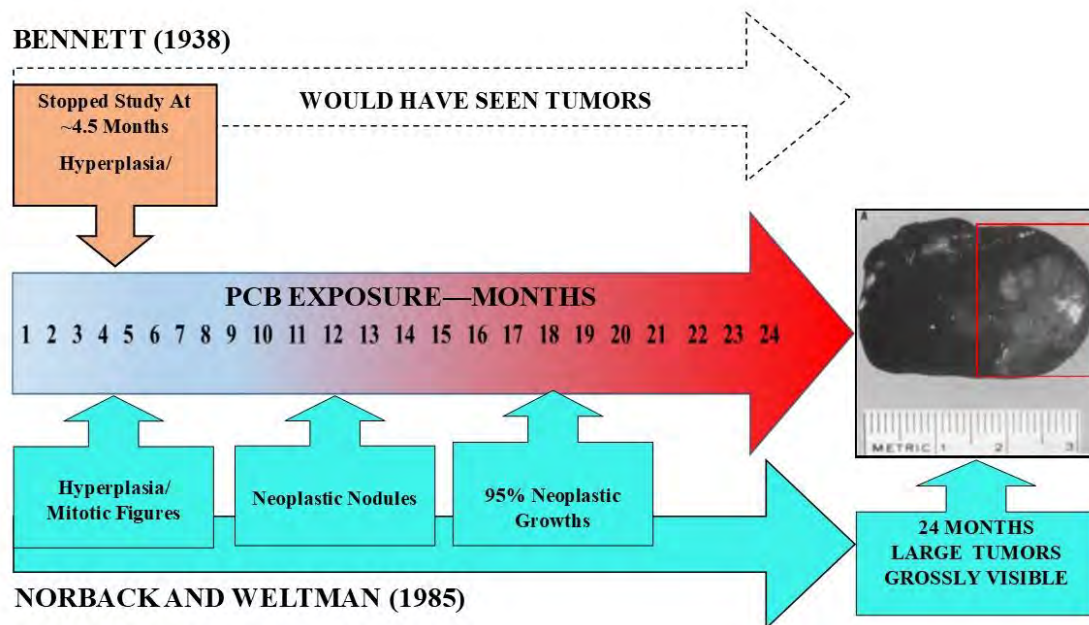
(arrows) is a repair response following hepatocyte loss secondary to treatment with a hepatotoxicant [liver toxicant].

The NTP recommends that in toxicity studies where more than a few mitotic figures are produced in response to a toxic chemical, the study should “grade” or score the increase in mitotic figures and report the results. “An increased frequency of mitosis is unusual; it should be documented whenever present and given a qualitative severity grade.” There is a limit to how many times a cell can divide (typically, 50–70); under normal circumstances, the cell simply dies once that limit is reached. This occurs through a process known as *programmed cell death* or *apoptosis*. However, in response to chemical carcinogens such as PCBs, the normal process of programmed cell death can be aborted, allowing the cell to become “immortal” (caused by complex carcinogen-induced genetic changes to specific genes in the DNA). This means that the damaged cell can now essentially divide forever forming a tumor mass giving rise to the hyperplasia Bennett[14] described in 1938.

The Bennett studies reported the same early hallmarks of cancer produced by PCB exposure as those described by Norback and Weltman in 1985.[28] But while Bennett terminated his experiment after only 3.5 months, Norback’s study was a lifetime PCB cancer study in which the pathological changes were followed over time until the animals were killed at 2 years. I illustrate the comparison by juxtaposing the Bennett findings at 3.5 months to the sequential tumorigenic steps described by Norback in Exhibit 10.

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Exhibit 10. Comparison of Bennett[14] Results with Norback and Weltman[28] Results



The most obvious hallmark of cancer is the high proliferation of liver cells in the early stages, which is termed hyperplasia and mitotic cell division. Both Bennett and Norback describe this event occurring during the early months of PCB exposure. Norback shows these early changes progress to tumors.

The focus on mitotic figures is not an esoteric aspect of cancer only used in basic research. Identifying and quantifying mitotic figures in biopsies taken from suspicious growths or palpable tumor masses are fundamental to clinical oncology practice. All pathologists specializing in cancer and oncologists treating cancer patients rely on the *mitotic index* to make important decisions (Ha 2016) regarding cancer patients' treatment and care.[33] The mitotic index is the most widely used metric to: 1) diagnose cancers; 2) stage cancers (determine how far the cancer has progressed); 3) assess a cancer's aggressiveness; and 4) make cancer prognoses. In clinical cancer practices, as well as in all fields of cancer research, the mitotic index is now a basic and routine measurement because it is the most useful and simple method for analysis of cell

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proliferation. Determining the mitotic index is a simple matter of counting the number of mitotic figures in tissue specimens within a prespecified area at low magnification.

3.2.6.1. 1939: Mitotic Figures Are Known Early Cancer Hallmarks

Although the mitotic index has been well-established as one of the most important tools in cancer research and clinical practice, and I have conducted extensive historical research into the state-of-the-science at the time, including what was known about mitotic figures and whether they were being interpreted as early indicators of cancer.

I have identified specific studies to highlight what was known at different time points regarding the pathological findings of mitotic figures and whether an objective Monsanto scientist would have identified them as early indications of cancer. Based on my research, I have concluded that a reasonable scientist conducting any toxicological animal experiment investigating pathological damage (in any organ) would have been well aware that mitotic figures were early hallmarks of cancer. The importance of mitotic figures was not only well-established as a toxicological indicator of cancer by the time Drinker published his first study in 1937, but the mitotic index was already widely used both in both general cancer studies and in clinical practice by those diagnosing and treating cancer patients. By 1939, hundreds of studies were clearly relying on the appearance of mitotic figures as the single *key* pathological hallmark for all types of cancers. From the more than 75 published studies and abstracts I reviewed, I have selected several key publications from 1889 to 1939 (when the last of the Drinker studies was published) as supporting evidence that the mitotic figures identified in the Drinker studies should have been interpreted as heralds of developing cancer. By 1939, mitotic figures were routinely used to: 1) identify cancers, 2) diagnose cancers, 3) quantify growth rates of cancers, and 3) make prognoses on likelihood of survival based on the type and aggressiveness of tumors.

In 1965, Triolo provided a well-researched and chronological construction of the history of cancer pathology studies, of which mitotic figures were the key visual identifiers, in his article entitled, "Nineteenth century foundations of cancer research advances in tumor pathology, nomenclature, and theories of oncogenesis." [34] He traced the first studies that recognized

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mitotic figures as important pathological features in cancer, which were published as early as 1889. At this early time point, scientists were observing fully developed tumors in which aberrant mitotic figures were under intense study:

The cytology of cancer was given special consideration by the peripatetic pathologist Edwin Klebs (1889) whose theory of cancer formation as a conjugation of epithelial cells and leukocytes largely grew out of the assumption that the neoplastic cell demonstrated a characteristically atypical (asymmetric) mitotic behavior [emphasis added] in which fragments of leukocytes participated. (The question of pathologic mitosis already had become a lively research issue...

Beginning in 1894, Houser published a series of studies advancing his conclusions regarding the cellular changes in skin cancer, of which mitotic “behavior” was a key feature. Triolo wrote:

In a series of articles (179-182) Hauser contended that connective tissue alterations were entirely incidental to the performances of the epithelium in the development of carcinoma...According to Hauser, cancerous degeneration was associable with a biologic disordering of the epithelium, in which the cells appeared to undergo a loss of normal physiologic function by virtue of derangements in the cellular and nuclear dimensions, chromatin content, mitotic behavior [emphasis added], and protoplasmic character.

By the early 1900s, cancer studies were so advanced that elegant studies were being conducted on tumor transplants to evaluate their survival and growth rates when tumors were grafted between species (typically between rats and mice). Mitotic figures were used to not only identify the transplanted cancerous cells but to track their growth rates in the host tissue. For example, Murphy and Nakahara published a study in 1920 that relied on mitotic figures to characterize the appearance of cancer and confirm transplanted tumor cells were indeed growing in the spleen.[35]

Spleen -The stimulation of germinal centers was manifest 48 hours after the blood injection. In a section taken at this stage an average nodule usually contained a few well marked mitotic figures [emphasis added], three to five as a rule, more rarely six or seven. All stages of mitosis [emphasis added] were easily

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distinguished...The frequency of mitosis [emphasis added] in the germinal center after 4 days was apparently greater than before (Fig. 1).

Exhibit 11 presents Figure 1 referred to in the preceding quote from Murphy and Nakahara.

**Exhibit 11. Figure 1 from Murphy and Nakahara (1920),
Germinal Center of the Spleen with Mitotic Figure[35]**

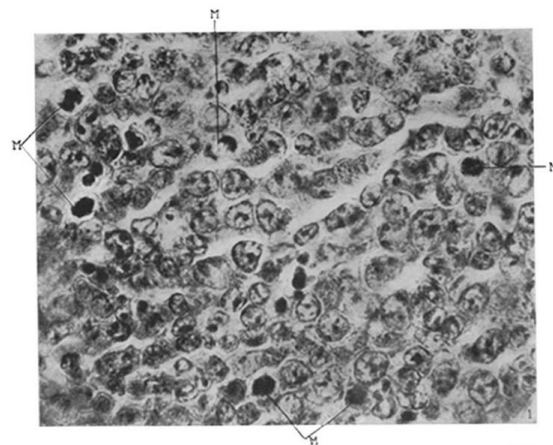


Fig. 1. Germinal center of the spleen 4 days after the blood injection. M, mitotic figure

In 1925, Ludford authored a lengthy treatise on “The general and experimental cytology of cancer.”[36] Combining his research with an extensive review of more than 50 published studies, he described key cellular hallmarks of cancer for research and clinical diagnosis purposes. Ludford’s extremely detailed descriptions of the appearance (morphology) of cancer cells includes many discussions of mitotic figures. Ludford, published his work more than a *decade* before Drinker’s first PCB study was published in 1937. Most notably, he discusses at some length the appearance of mitotic figures as a key feature in developing tumors. Ludford extended his discussion of mitotic figures to identify both normal mitotic figures (that appear in the early cancer stages) to aberrant mitotic figures (that appear in fully formed malignant tumors). His detailed drawings of mitotic figures are no different from those used today by toxicologists in cancer studies to identify different stages of cancer.

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One of Ludford's schematic drawings is presented in Exhibit 12, and it is noteworthy that his review is one of the first publications to correct the previous misconception that tumors develop from aberrant mitotic cell division. Ludford correctly concluded that while aberrant mitotic figures are present in tumors, cells with atypical mitoses are aborted and die because they are so damaged and compromised that they cannot undergo further cell division and contribute to the tumor mass. In other words, aberrant mitotic figures have no diagnostic importance. The total number of mitotic figures is the only important feature needed to identify cancerous tissue.

**Exhibit 12. Figure 13 from Ludford (1925),
 Variations in the Mitotic Process in Cancer Cells[36]**

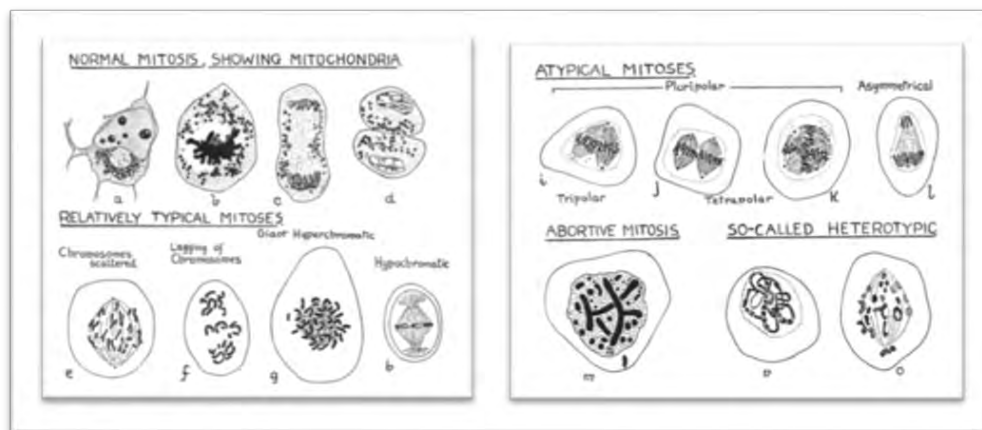


Figure 13. Variations in the mitotic process in cancer cells

On this topic, Ludford concluded that mitotic abnormalities do not contribute to tumor growth and that they are secondary results of tumor growth.

The experimental investigation of the conditions favouring [sic] abnormal mitosis, together with the observation of cells in tissue cultures, indicate, then, as Ewing says, that the abnormalities are secondary results of tumour [sic] growth, and not primary and essential.

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He discussed the frequency of detecting normal and abnormal mitosis with regard to establishing the growth rate of tumorigenesis, which is the key indicator of the aggressiveness of different cancer tumors, as follows:

The frequency of occurrence of abnormalities in mitosis is subject to a great deal of variation. Usually in slow-growing tumours [sic] there are relatively few mitoses, and these are of the normal type, but with more rapid growth the mitotic figures are more numerous and exhibit abnormalities, especially where degeneration occurs, and where there is a marked inflammatory reaction.

Ludford noted that the mitotic figures are more numerous when *degeneration* and *inflammation* reactions occur in damaged organs. This is noteworthy because Drinker's findings included both degenerative changes and inflammation in the PCB rat livers. In 1935, Mendelsohn reconfirmed that mitotic figures alone were the only hallmark necessary to identify cancers (abnormal mitotic figures were not important for diagnosis of developing tumors).[37]

At the present time asymmetrical divisions are not considered to be diagnostic for malignancy, but their occurrence in malignant tissues is not disputed. Some animal tumors are characterized by many abnormal figures and others by a smaller number, but there is none in which abnormal figures have never been found. Their presence in normal regenerating and inflammatory tissue seems to have been accepted by many investigators. However, a review of the literature will reveal that the occurrence of abnormal mitoses in normal tissues is still a moot question; if they are present they must be rare. Levine (1931) has published a comprehensive review with especial emphasis on mitosis in cancer cells.

The point that Bennett would not have had to conduct a sophisticated, lengthy, and time-consuming pathological investigation of the complex morphology of mitotic figures, differentiating normal and abnormal mitotic figures. The sole finding of mitotic figures was sufficient to cause concern that PCBs were carcinogenic.

By 1937, counting the number of mitotic figures was so established and routine that clinical pathologists were relying on this diagnostic feature as the sole cancer hallmark to estimate survival rates from tumorous growths. For example, in the same year Bennett published his first

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study (1938), Casey published a study investigating the prognostic value of using the mitotic index to evaluate both the longevity and mortality associated with lymphosarcoma tumors (lymphosarcomas are among the group of non-Hodgkin lymphomas that IARC has linked to PCB exposures).[38] In his introduction, Casey noted that the mitotic counts for the primary tumor, metastases (secondary tumor that has traveled to another organ), and recurrent tumors had the same mitotic index as biopsy tissue. Using the mitotic index had now become such a standard and routine pathological practice in 1937 that Casey was able to rely solely on this single criterion to differentiate between malignant and benign tumors. Furthermore, he concluded mitotic counts in animal tumors were similar to those in human tumors:

The evidence obtained indicated that the primary tumor, the metastases, and the recurrences had the same mitotic coefficient [emphasis added] in biopsy material. Autopsy specimens have not been studied sufficiently. Tumors of man have been found to have mitosis counts [emphasis added] similar to the tumors of other mammals. Malignant tumors have shown more than 4 mitoses per 1000 tumor cells and benign tumors less than 4 mitoses per 1000 tumor cells, irrespective of type, site, and mammalian species.

Casey's results of the mitotic counts (column in red rectangle) in various tumor biopsy specimens versus patient longevity are presented in 0.

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**Exhibit 13. Table I from Casey (1937),
Prognostic Value of Mitosis Count in Lymphosarcoma[38]**

	Pathology number	Sex	Age	Duration of Symptoms (Months)	Mitoses per 1000 Tumor Cells†	Site of Origin	Longevity‡ (Months)
1	B 8177	M.	88		8.0(10-7)	Tonsil	D 50.0
2	B 8826	M.	38		28.0(10-7)	Neck	D 6.7
3	B 8948	M.	29		46.0(10-6)	Nasopharynx	D 0.8
4	B 9065	F.	49		10.0(10-6)	Abdomen	D 13.5
5	B 10648	F.	59		11.0(10-6)	Tonsil	D 64.0
6	B 10982	M.	67	5.0	18.3(12-7)	Tonsil	D 7.6
7	C 1181	M.	53		27.0(10-7)	Humerus	D 21.0
8	C 2562	F.	4		5.0(10-7)	Trapezius	D 7.5
9	C 3227	M.	7	6.0	41.0(10-7)	Ileum	D 1.0
10	C 3713	M.	40	4.0	4.0(10-7)	Ant. Triangle	D 30.5
11	C 4409	M.	52	10.0	3.0(10-7)	Tonsil	L 66.0
12	C 4575	M.	60	18.0	39.0(10-7)	Neck	D 1.0
13	C 4696	M.	62	24.0	9.0(10-7)	Neck	D 46.0
14	C 4889	M.	31	24.0	2.0(10-5)	Axilla	L 66.0
15	C 6318	M.	40	30.0	11.0(10-7)	Neck	D 7.2
16	LTR 8	M.	22		12.9(14-10)	Retroperitoneal	D 3.9
17	LTR127	F.	65	24.0	0.0(10-7)	Rectum	D 35.0
18	LTR128	M.	53	24.0	6.8(25-15)	Cecum	L 66.0
19	LTR129	F.	11	5.0	5.0(10-6)	Cecum	L 66.0
20	LTR139	M.	49	4.0	15.0(10-6)	Parotid	D 7.0
21	LTR148	F.	62		29.0(10-4)	Neck	D 0.9
22	LTR168	M.	51	11.0	9.3(14-9)	Groin	D 2.1
23	LTR188	M.	45	2.0	16.9(16-11)	Nose	D 2.3
24	LTR205	F.	65	7.0	3.0(10-7)	Neck	D 57.0
25	LTR202	M.	33	3.0	3.3(12-5)	Groin	L 66.0
26	LTR208	F.	70	5.0	17.0(10-7)	Tonsil	D 37.0
27	LTR211	M.	72	4.0	33.3(12-7)	Neck	D 5.7
28	LTR223	M.	56	2.0	15.0(10-7)	Mesentery	D 0.8
29	LTR239	F.	54		12.0(10-6)	Tonsil	D 7.7
30	LTR261	F.	9	3.0	28.0(10-7)	Axilla	D 5.8
31	LTR263	M.	42	8.0	20.0(10-5)	Tonsil	D 7.6

Finally, Casey concluded the following:[38]

A high and significant correlation was found between the mitosis count in biopsies of lymphosarcoma and the longevity and mortality from the tumors after biopsy. The study was objective in that the diagnosis was made by others and the clinical outcome was not known to the author at the time the mitosis count was made.

This conclusion was based on the results of mitotic coefficients versus mortality at different survival times, as show in Exhibit 14:

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**Exhibit 14. Table III from Casey (1937),
Mortality from Lymphosarcoma for Various Mitotic Coefficients[38]**

Mitoses per 1000 Tumor Cells	Interval	Cases	Mortality at One Month after Biopsy	Mortality at Six Months after Biopsy	Mortality at Twelve Months after Biopsy	Mortality at Three Years after Biopsy	Mortality at Six Years after Biopsy
0-3	4	5	0%	0%	0%	20%	40%
4-11	8	10	0%	10%	30%	50%	80%
12-27	16	9	11%	33%	77%	100%	100%
28-59	32	7	57%	100%	100%	100%	100%

In addition to these cancer studies and use of the mitotic index in all areas of oncology and clinical pathology, mitotic figures were the key morphological feature of studies on *chemically induced* cancers. By 1939, many studies had been published in which counting mitotic figures allowed scientists to detect the early stages of cancer and follow tumor development induced by *chemical carcinogens*. For example, Morton et al. (1936) investigated benzene-based chemicals triphenylbenzene and tetraphenylmethane isolated from coal tar, and showed they were carcinogenic in animal studies.[39] They described the tumor mass as follows:

The cells show variations in size, shape, and staining reaction, the cytoplasm being rather uniformly strongly acidophilic, while the nuclei tend to be large, clear and vesicular, and show considerable variation in size and shape. Numerous irregular mitotic figures [emphasis added] are encountered and not infrequently very large cells are noted... Cells comprising this infiltrating mass tend to be rather large, clear and vesicular in character, the nuclei being particularly irregular in size and shape. Mitotic figures [emphasis added] are encountered.

Barnes and Furth (1937) conducted cancer investigations in laboratory animals by exposing them to benzpyrene (a benzene-based compound), another carcinogen isolated from coal tar.[40] When injected into the spleen, benzpyrene caused cancer of the blood cells. When these

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malignant cancer cells circulated in the bloodstream, they lodged in the liver, where they were identified based on their mitotic count. In other words, Barnes and Furth followed the path of cancer cells created in the spleen and transported to other organs using only mitotic counts to identify the malignant blood cells (emphasis added):

The liver showed moderate diffuse and perivascular infiltration similar to that shown in Fig. 20. The malignant cells occurred singly or in groups of from four to fifteen scattered throughout the sinusoids. Mitotic figures were numerous [emphasis added]...Microscopically the subcutaneous tumor was composed of the atypical cells already described. Mitotic figures [emphasis added] occurred in vast numbers, so that as many as nine were found in one field viewed at 900 X magnification.

In 1939, Brues et al. designed a clever experiment to investigate the “cancer potency” between similar carcinogens to determine the precise molecular chemical structure that made one carcinogen more potent than a slightly different carcinogen.[41] This was an investigation delving into the possibility that the *potency* of chemical carcinogens was somehow linked to the latency between the beginning of exposure and when the tumor first appeared. The researchers postulated that more potent chemical carcinogens would have a shorter latency period than did weaker carcinogens. As in previous carcinogen studies, they used the mitotic index to identify developing tumors caused by carcinogens with slightly different chemical structures:

Most mice were killed after tumors had reached considerable size and paraffin sections were made. Mitoses were enumerated in groups of 1000 [emphasis added] or more counted tumor cells...In the 3 groups in which mitosis counts [emphasis added] were done, they were seen to show a good degree of correlation with growth rate. Here, again, it was not possible to demonstrate such correlations in individual instances, but only by groups.

Brues et al. found a correlation between the potency of the different chemical carcinogens and the latency period, summarizing:

There is a high degree of correlation between the malignancy of chemically induced tumors, as measured by growth rate and mitotic index [emphasis added], and shortness of the latent period before appearance of palpable tumors. This

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relation holds true in the various responses of different strains of mice to the same agent, and in responses to different agents and modes of administration.

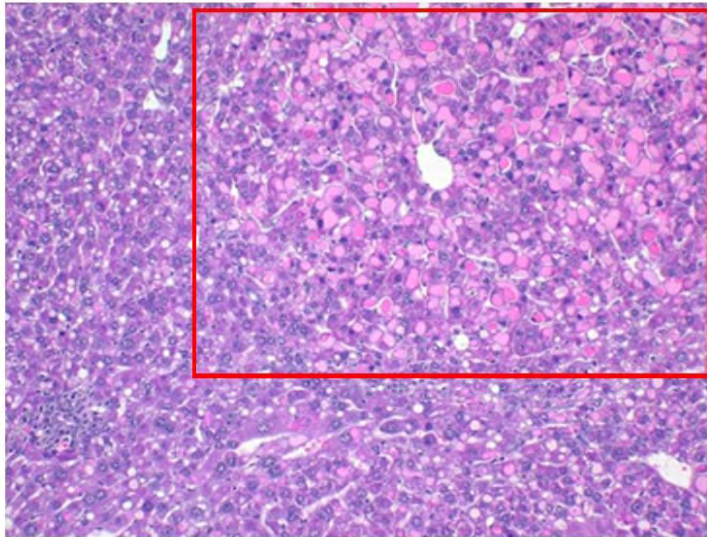
In summary, the historical studies previously described clearly show that the general state-of-the science regarding the importance and significance of mitotic figures as early hallmarks of cancer was well established a decade before the Bennett studies were published. Many toxicity studies published in the 1930s considered mitotic figures to be the most obvious and key pathological feature of cancer.

3.2.7. 1939: Mitotic Figures Were Cancer Hallmarks

In addition to mitotic figures, the other pathological hallmark of cancer emphasized by Bennett was *hyaline bodies*. Scientists studying these structures in cancerous tissue also referred to them as *hyaline inclusions* or *droplets*. A microphotograph produced by the National Institute of Environmental Health Sciences (NIEHS) as part of its Digitized Atlas of Mouse Liver Lesions shows hyaline bodies, which are readily identified in this image as numerous light pink-staining liver cells (Exhibit 15).[42]

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**Exhibit 15. National Institute of Environmental Health Sciences
Photomicrograph of Hyaline Bodies[42]**



Source: https://www.niehs.nih.gov/research/resources/visual-guides/liverpath/degenerative/hyaline_bodies/index.cfm

NIEHS describes hyaline bodies as being seen in liver degeneration, as well as in hepatocellular neoplasms. Despite Bennett's reporting that hyaline bodies are characteristic of the pathological changes that occur with PCB exposures,[14] Monsanto's scientists conducted no follow-up studies to determine the eventual outcome of these damaged cells. That is, since hyaline bodies can be evidence of degeneration or developing cancers, Monsanto should have confirmed whether the livers would develop tumors. It is now well-known that PCB exposure is associated with developing hyaline bodies and that cancer does indeed develop with prolonged PCB exposure.

These bodies have more recently been studied to determine the composition of the hyaline material that builds up in cancerous liver cells. In 1999, Stumptner et al. published a detailed study of these structures, describing both the morphology and composition of these malignant structures.[43]

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HCC cells [hepatocellular carcinoma cells; liver cancer cells] may contain a variety of intracytoplasmic inclusions differing in morphology and chemical composition....However, IHBs...[intracytoplasmic hyaline bodies] so far evaded further characterization. The HCC case presented in this communication was exceptional as IHBs were particularly numerous in the tumor cells allowing further analysis of this material.

It is my opinion that, like mitotic figures, hyaline bodies were well-established as morphological indicators of liver cancer at the time Bennett published his studies. To support this opinion, I conducted a similar historical literature review to establish a timeline showing when these hallmark cancer structures were first identified in tumor cells, when it became common or general knowledge, and when they were routinely used as visual indicators to identify liver cancers. The following sections highlight just a few of the numerous published studies that were published well before the Bennett studies were completed.

In the previously described 1965 Triolo review in which he detailed the use of mitotic figures for identifying cancerous tissues,[34] Triolo stated that hyaline bodies were first reported by Muller as early as 1836 as being a specific and morphologically distinct category of cancer.

Muller's results, a part of which were reported as early as 1836...prompted him to reject the Laennecean concept of heterologous tissues and to adopt a cellular basis for tumor taxonomy. He distinguished according to cell type, (a) fibrous or scirrhus cancer, (b) reticular cancer, (c) alveolar or colloid cancer, and (e) hyaline cancer. [Emphasis added.]

One of the first published studies that referred to hyaline bodies in cancer was “An address on characteristic organism of cancer” by Russell in 1890.[44] He reviewed numerous studies and reported the following:

“Professor Klebs published, in June of this year...papers "On the Nature and Diagnosis of Cancer Formation," in which he discusses these questions with fairness and masterliness [sic]. In them he refers to hyaline bodies [emphasis added] present in cancer, which, however, he is decidedly disposed to regard as degenerative products... I am, however, disposed to regard most of his hyaline bodies [emphasis added] as productions of the cells, for hyaline masses [emphasis

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added] are frequently present, and are easy of recognition [emphasis added] in the alveoli of the more adenomatous cancers...

Hyaline bodies were some of the most obvious hallmarks used in clinical practice to identify tumors in biopsy tissue or excised livers tumors. For example, Keen (1899) reported his findings of a liver tumor mass he removed from a patient that had the following appearance:[45]

Immediately adjacent to this wall begins the extensive necrotic change which permeates the whole tumor. It would seem that fully 80 per cent. of the tumor mass, if not more, is made up of cellular detritus, caseous, or hyaline material. [Emphasis added.]

By 1925, it was well-established that malignant cancers develop in tandem with degenerative changes for some chemical carcinogens. That is, while some chemical carcinogens only produce cancerous tumors (with only slight evidence of cell damage), some carcinogens produce both severe *degenerative* changes that occur in tandem with malignant cell growth that eventually lead to tumor formation. PCBs fall into the latter category. Ludford stated that while investigating tumors, areas of degeneration are common.[36]

Since areas of necrosis [cell degeneration] are of common occurrence in tumours, all stages of cellular degeneration are seen in histological sections.

In tumors, cells undergoing degeneration form intracellular hyaline bodies and become one of the distinguishing features of the tumors themselves. They are easily visible with common stains used in the laboratory (as shown in Exhibit 15 with the pink-stained cells):

Retrogressive changes in the ground cytoplasm often result in the formation of granules of different kinds, and hyaline droplets. [Emphasis added.] Some of these products of cytoplasmic degeneration exhibit special affinities for stains. Hyaline droplets [emphasis added] stain specially with fuchsin, and were at one time regarded as cancer parasites.

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Ludford stated that hyaline bodies by themselves may not be specific to cancer but that since degeneration occurs in tumors, they are one characteristic that can be used to follow developing tumors.

Hyaline bodies were characteristic clinical diagnostic indicators of tumors produced by chemical carcinogens. Twort and Twort (1935) conducted a series of experiments to evaluate whether carcinogens would produce tumors when directly applied to organs.[46] They explained their investigations in which they applied carcinogens to the surfaces of different organs. They then evaluated those organs for the presences of cancer hallmarks or “special features,” including hyaline bodies. They stated:

The organs with which we shall deal are the skin, liver, spleen, thyroid, parathyroids, brain, and pituitary gland. The special features relating to the organs with which we are at the moment concerned are...

Liver: Presence of fatty infiltration (condition X) and hyaline degeneration. [Emphasis added.]

Spleen: Size of organ and presence of hyaline degeneration. [Emphasis added.]

Thyroid: Size of organ, presence of hyaline degeneration [emphasis added], colloid and parathyroid.

Twort and Twort used different benzene-containing synthetic hydrocarbon carcinogens to produce skin cancer. The diagnostic feature used to identify malignant skin cancer tumors was hyaline bodies, as shown in their table, which is presented in 0.

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**Exhibit 16. Table 11 from Twort and Twort (1935),
 Effect of Three Hydrocarbons on the Spleen[46]**

Agent	No.	Per cent Large	Per cent with Hyaline Degeneration
H. C. 7	378	20	19
H. C. 8	162	42	54
H. C. 9	51	59	69

I continue this discussion of hyaline bodies as hallmarks of cancer in my discussion of the Miller (1944) PCB study in section 3.3 below.[17]

In summary, mitotic figures and hyaline bodies were used as primary indicators of the early stages of cancer and to follow the progression of tumorigenesis well before the Bennett study was published.

Even if Monsanto's toxicologists did conclude, after reviewing Bennett's findings, that they only represented degenerative liver damage, the fact that the severe and extensive degenerative pathological lesions were still present in animals that were allowed to recover for 2 months after PCB exposure was stopped should, by itself, have triggered further studies. If longer exposure studies had been performed ostensibly only for the purpose of following the progression and outcome of the "degenerative" lesions, Monsanto's scientists would have found tumors in the livers, even if the intended purpose of the study was not to identify PCB-induced tumors.

3.3. 1944: Dr. Miller

Miller J.W. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Public Health Reports. 1944; 59(33):1085–1093.[17]

Like the Bennett study,[14] the 1944 Miller PCB exposure study[17] should have been another trigger for Monsanto to have conducted long-term animal cancer studies.

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By 1939, when the last of the three Drinker studies was published,[24] there was no uncertainty that PCBs caused severe and long-lasting systemic liver damage and initiated the early steps in tumorigenesis. However, because the Bennett studies were essentially *cause of death* applied toxicity studies, there were several fundamental and basic toxicity questions that needed to be addressed. For example, the Bennett studies only focused on the liver because the Halowax workers died of liver disease, but could PCBs also produce toxic effects in other organs? Since the Bennett studies only investigated the effects in the liver, their results could not be used to answer questions about toxicity/cancer in other organs.

The Bennett studies only used rats, so it was also not known whether rats were the most sensitive or were representative of human toxicity (most well-designed basic toxicity studies use multiple test species). To address outstanding questions, the US Public Health Service conducted a series of very robust toxicology studies that confirmed and extended the Bennett's results regarding PCB toxicity. If Monsanto's toxicologists had any outstanding questions after carefully reviewing the Drinker studies, they could not claim as much after reviewing the Miller study in 1944.

The Miller study was published not in an obscure or rarely read scientific journal, but rather in a National Institutes of Health, Public Health Report, based on research conducted in the Industrial Hygiene Research Laboratories—a highly regarded publication by industrial hygienists in all fields of chemical manufacturing operations.

In 1944, Dr. Miller, who was a Surgeon with the United States Public Health Service (US PHS; founded in 1798, it is the oldest governmental health agency), published the results of numerous toxicity studies that were conducted with a commercial Aroclor (Aroclor 1242). As a doctor employed in the US PHS, Dr. Miller's professional responsibility as a US PHS officer was to monitor and identify potential health threats posed by industrial chemicals to the general public and workers. That is, he was responding to empirical work-related evidence that PCBs were already causing health-related problems and could represent an emerging health threat to workers and the public.

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While Dr. Miller published the Aroclor study, the experiments were actually conducted in the US National Institutes of Health, Industrial Hygiene Research Laboratories, by Surgeon B.J. Jones and Physiologist D.D. Donahue. Miller's study significantly extended the Drinker findings for the following reasons:

1. Animals were exposed to a pure commercial biphenyl: Aroclor 1242;
2. Multiple animal species were exposed to the Aroclor (rats, mice, and guinea pigs);
3. Animals were exposed via multiple exposure routes;
4. All major organs were examined for pathological damage; and
5. It provides direct evidence that PCB-induced pathology included the early hallmarks of cancer, not only in the liver but in the immune system (Drinker did not investigate any changes related to blood cancers).

While the Miller study investigated PCB-induced damage in all organs, the pathological lesions reported specifically for the liver were nearly identical to Bennett's description of the lesions. This supports my conclusions regarding the severe damage produced by formulations that included PCBs, as discussed for the Bennett studies.

Dr. Miller was very clear in clarifying the purpose of his study:

The demands of industry as a result of the war have greatly increased the use of chlorinated naphthalenes and chlorinated diphenyls. In the past few years the hazards associated with their application have attracted much interest and a number of reports regarding the systemic and dermatologic effects of exposure, including fatal cases, have been made.

He also emphasizes that his study would only focus on Aroclor 1242 (to avoid any confusion regarding the interpretation of his toxicological results):

Only the pathologic changes in animals exposed to a commercial chlorinated diphenyl [Aroclor 1242] are given here.

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Miller noted that there was a consistent pattern of damage among the different species he tested and that it always involved the liver:

Two conspicuous pathologic findings were observed-liver damage in all series of experiments and skin changes in the animals receiving subcutaneous injections or applications of the material to the skin.

Interestingly, he identified a different sensitivity between toxic responses to PCBs among guinea pigs, rabbits, and rats:

It was possible to detect a difference in response of the three species to the material on the basis of liver damage. Most liver damage was found in the guinea pig, less in the rabbit, and least in the rat. This same species order was followed, regardless of dose, duration of test, or mode of administration.

The importance of this finding is that is not clear what species best represents humans. If guinea pigs are the best representatives of the human toxic response, Bennett's studies likely *underestimated* the PCB toxicity since the Bennett studies only used rats.

Miller cites the previous Drinker studies and concludes the specific PCB-induced pathological changes in the liver first reported by the Bennett study,[14] in which the pathology was reported for a *mixture* of chlorinated diphenyls [PCBs] and naphthalenes), were nearly identical to the pathological lesions he found on exposing rats to pure Aroclor 1242. As did Bennett, Miller identified hyaline bodies as one of the major *unique* PCB-induced pathological lesions in the liver, stating:[17]

Intracellular hyaline bodies were found in the liver of the rat alone...They occurred in from 20 to 38 percent of the animals treated in the various ways. They were somewhat less marked in degree and in number of animals when the chlorinated diphenyl was ingested. These findings agree with Bennett who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds. [Emphasis added.]

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Miller went on to discuss the importance, appearance, and interpretation of PCB-induced hyaline bodies with regard to the hallmarks of cancer:

The hyaline bodies are morphologically different from those produced by butter yellow in hepatic tumor cells. They probably represent further development of the same general type of hyaline degeneration as has been observed with certain azobenzenes.

This is a very important statement because it compared the appearance of pathological hyaline bodies to known animal and human carcinogens, which were the azo-dyes. It was well known throughout the scientific community by 1944 that azobenzene compounds were used as dyes and cause cancer. In fact, the very first long-term animal study investigating chemical carcinogenesis was conducted more than a decade earlier on azobenzenes—namely, o-aminoazotoluene. In this groundbreaking study by Yoshida in 1932,[47] who is credited with performing the seminal lifetime cancer study in laboratory animals, he dosed animals with azo dyes.

This single study heralded an explosion of cancer studies in the 1930s and 1940s investigating chemical carcinogens. This was noted by Orr and Stickland (1941):[48]

“The production of liver tumours [sic] in rats by the inclusion of azo-dyes in their diet was first demonstrated by Yoshida [1932; Sasaki & Yoshida, 1935]. In this work the dye used was o-aminoazotoluene (2:1:1:4:3-tolueneazoaminotoluene).

If Monsanto scientists were not convinced that hyaline bodies were important triggers for cancer after reviewing the Bennett study, the suggestion that PCBs caused pathological lesions similar to azo compounds, which were known animal *and* human carcinogens, should have convinced Monsanto that cancer studies were certainly necessary to address this new finding by Miller.

It is clear that Miller considered hyaline bodies to be the most important pathological lesions produced by PCB in the livers of rats because the only photomicrograph he included in his work is a group of hyaline bodies. It is common practice for scientists to include photomicrographs only for the most important features of a study. While Miller reported many pathological lesions, he only showed the one lesion he thought important. That photo is shown below in Exhibit 17.

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**Exhibit 17. Plate I from Miller (1944),
Intracellular Hyalin Bodies in Livers of rats Exposed to a
Chlorinated Diphenyl[17]**

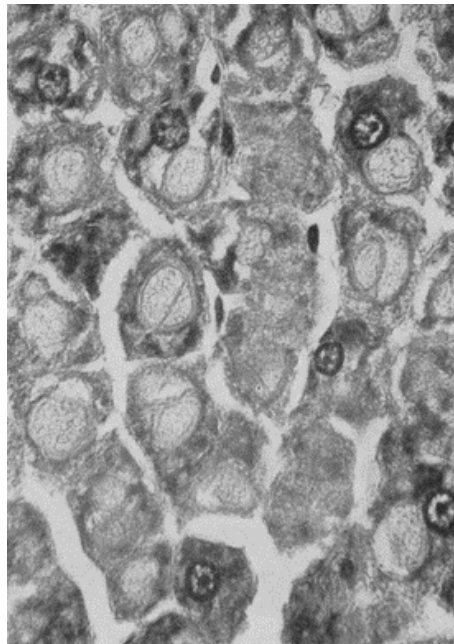


Plate I. Figure 1. Intracellular hyaline bodies in livers of rats exposed to a chlorinated diphenyl.

Another important aspect of Miller's work is that he reported the pathology for three species, exposing the animals through numerous routes of administration. The pathology was "conspicuous" and consistent. He summarized as follows:

Guinea pigs, rats, and rabbits were exposed to a commercial chlorinated diphenyl by subcutaneous injections and applications to the skin. The material was also administered to guinea pigs and rats by ingestion and to rats alone by corneal instillations. The doses varied from 17 to 1,380 mg. and were either single or were repeated at regular intervals.

Two conspicuous pathologic findings were observed-liver damage in all series of experiments and skin changes in the animals receiving subcutaneous injections or applications of the material to the skin.

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Fatty degeneration and atrophy of the centrilobular cells were present in varying amounts and in varying numbers of animals the different test groups. In the rat an additional finding, hyaline bodies within the liver cells, was noted in certain animals.

Miller also specifically highlighted the fact that the pathological changes were unique to PCBs and emphasized the species difference in sensitivity:

Attention is called to the fact that the chlorinated diphenyl used in the above experiments produces liver changes in the rat having marked differences from those resulting from other toxic substances and that such changes were not found in the guinea pig and rabbit... It was possible to detect a difference in response of the three species to the material on the basis of liver damage. Most liver damage was found in the guinea pig, less in the rabbit, and least in the rat.

Finally, Miller also for the first time identified evidence of cancer not yet reported by Bennett.

Miller reported PCB-induced early evidence of lymphomas in the guinea pig, stating:

Changes in the spleen were essentially the same except that lymphoid hyperplasia was more frequent and few to moderate numbers of hemosiderin-bearing cells were seen in 12 of 23 animals.

Which was also seen in rabbits:

The changes noted were slight to marked congestion of the cavernous veins and slight to moderate follicular lymphoid hyperplasia.

If, for any reason, Monsanto was confused or unconvinced about the import of studies conducted prior to Miller's work, his conclusions left no room for uncertainty. Monsanto should have conducted chronic exposure studies to investigate the effects of long-term exposure to PCBs.

4. MONSANTO'S PCB STUDIES FAIL TO ACCOUNT FOR CHRONIC EXPOSURE

Monsanto used contract laboratories to conduct PCB studies from 1934 to 1972. However, not one of these studies was conducted according to the generally accepted standards in the field of toxicology that could be used to derive safe exposure levels to protect the general public. Furthermore, the chronic animal testing Monsanto conducted after 1970 is not credible.

I conclude that Monsanto produced scant relevant, applicable, or credible toxicity information in any of its studies. With very few exceptions, Monsanto did not share any toxicity information with the general scientific community, nor was it peer reviewed or published in any scientific journals.

4.1. With few exceptions, most well-designed, long-term PCB cancer studies have shown strong evidence of cancer.

The protocols used in cancer studies by the mid-1940s were standardized and did incorporate the important features necessary to identify chemical carcinogens, as is evidenced by the fact they did detect cancer. The results and conclusions of the pre-1970 cancer studies have withstood the test of time, and chemicals identified as carcinogens in the 1930s are still considered carcinogens today.[11], [12] Had Monsanto conducted cancer tests for PCBs at that time, the tests would have shown what later tests made clear—that PCBs are carcinogens.

With few exceptions, most well-designed, long-term PCB cancer studies have shown *strong* evidence of cancer as I showed in the EPA Exhibit 5 and Exhibit 6. The evidence of carcinogenicity was so strong in these studies published by independent scientists that it was persuasive to non-toxicologists serving in Congress. It was Congress that banned PCBs in 1976 and not based on EPA scientist's recommendations. For example, a 1976 EPA press release stating why PCBs were being banned, states specifically noted they *caused cancer in animals* (<https://archive.epa.gov/epa/aboutepa/epa-bans-pcb-manufacture-phases-out-uses.html>):[49]

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PCBs have caused birth defects and cancer in laboratory animals, and they are a suspected cause of cancer and adverse skin and liver effects in humans. EPA estimates that 150 million pounds of PCBs are dispersed throughout the environment, including air and water supplies; an additional 290 million pounds are located in landfills in this country.

It is important to note that EPA does not state that PCBs are “suspected” animal carcinogens, but they “caused” cancer in laboratory animals.

I carefully reviewed Monsanto’s own cancer study protocols that were developed by IBT and were used to test the carcinogenicity of different Aroclors—there is *nothing* new in its study design that could have not been used by the mid-1940s. Indeed, the same study design used in the later Monsanto studies could have been used by Monsanto in the 1930s, 1940s, 1950s, or 1960s. It is my opinion that *if* Monsanto did conduct lifetime animal cancer studies on each of its Aroclor products (namely, Aroclors 1242, 1016, 1248, 1254, and 1260), those studies would have shown that PCBs were carcinogenic in animals. Most of the studies that were conducted in the 1970s and 1980s, which EPA summarizes in its tables, were positive and show PCBs were animal carcinogens. These studies could have been carried out in the mid-1940s and they would have shown that PCBs were carcinogenic. There is no compelling reason to believe that if those studies were performed prior to the 1970s and 1980s the results would have been significantly different.

I should also stress again, that in evaluating different cancer studies, positive cancer studies carry much more weight than negative studies, for the simple reason that it is easy to conduct a so-called *bad* cancer study that does not show cancer, but it is nearly impossible to force tumors to develop for a chemical that is not a carcinogen. Moreover, negative cancer results are never evaluated separately from positive cancer studies. For example, there are people who are chain smokers and who will smoke until they die but will not develop lung cancer. This negative finding cannot be interpreted to mean that the carcinogens in cigarette smoking do not cause lung cancer.

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4.2. It is not the number of PCB studies but the type of studies that determine toxicity and carcinogenicity.

Monsanto conducted only 165 laboratory studies on numerous compounds Monsanto was developing or manufacturing. None of the studies on PCBs can be considered *toxicity studies*; rather, they were lethality studies.

Monsanto conducted only 79 studies on pure biphenyl Aroclor and these studies were crude LD50 studies--not toxicity studies. In fact, there was *zero* data in any of the 79 studies that could be used to derive an acceptable safe chronic exposure level for either workers or the general public (with the exception of the Drinker[24] study that proposed workplace air levels, but that study may not be applicable because it was a subchronic study and they evaluated a mixture of chlorinated compounds). I am aware of no Aroclor study that was relevant to actual anticipated human exposures.

The remaining Monsanto studies are toxicity studies on complex Monsanto mixtures that contained different amounts of PCBs along with other toxic compounds. For example, Pydraul contains organophosphate esters and PCBs. When animals were exposed to Pydraul it is not possible to extract the specific toxic effects contributed by PCBs or organophosphate esters from the overall toxic effect observed in the study. The Pydraul toxicity studies are relevant to sites where Pydraul exposures have occurred, but not to sites where Aroclor exposures are the focus. This being said, even if the confounding influence of the complex mixtures could somehow be untangled, these remaining studies would still be unusable for evaluate the chronic exposures associated with PCB either in the workplace or for the general public.

In summary, Monsanto conducted *no* credible toxicology study that is relevant and useful for determining the systemic toxicity from chronic exposures prior to 1970.

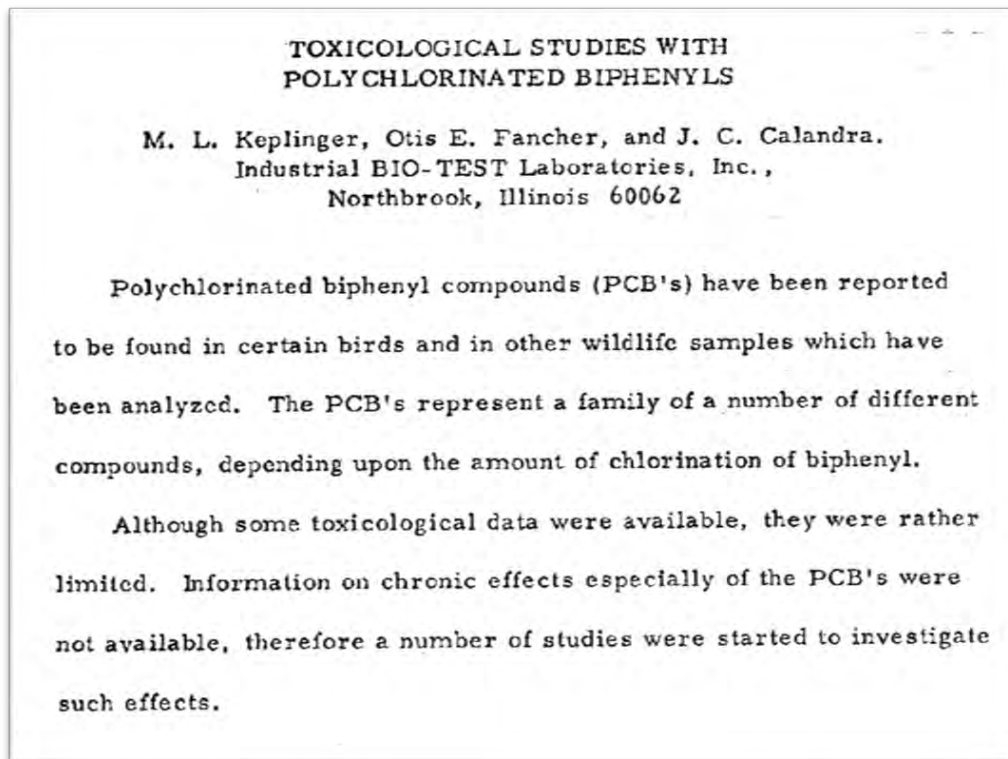
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4.3. The studies commissioned by Monsanto in the 1930s through the 1960s were not applicable to the evaluation of human toxicity for Monsanto's workers or the general public.

Monsanto generated little toxicology information and what they did generate was largely unusable. The president and principal scientists of Monsanto's own toxicology contract laboratory's statements support my opinion. Prior to 1966, Monsanto had consistently used the Younger Laboratory to conduct crude single dose studies on lethality and also to assess skin and eye irritation from very short-term exposures. When Jensen published his watershed study in 1966 confirming that extensive PCB environmental contamination had occurred from uncontrolled releases of PCBs from 1930–1966,[50] Monsanto retained another toxicology group: Industrial Bio-Test Laboratories (IBT). The first task for IBT was to evaluate the existing toxicity studies Monsanto conducted prior to 1970 to determine the quality and extent of toxicity information Monsanto had for PCBs. In one of the first toxicology reports produced by IBT (Bates 0531555; TOXSTUDIES0996) the cover page reads (Exhibit 18):[51]

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Exhibit 18. Cover Page from IBT Study (TOXSTUDIES0996)[51]



This indicates that Monsanto's toxicity information was "limited," which would have been a generous characterization based on my assessment. More importantly, it states that there was no chronic toxicity information available, which is consistent with my opinion.

In summary, not one of the studies conducted on Monsanto PCB Aroclors was applicable for long term exposure to PCBs in the workforce or general public.⁷ The contract studies only produced information on the lethal dose and short-term irritation—i.e., the quantity of PCBs that could cause death and qualitative information on short-term irritation effects on the skin and eye. Chronic toxicity information is vital for widespread contaminants like PCBs because exposure is

⁷ Note, I also reviewed the Treon study, which was poorly designed and implemented such that its results are not helpful.[122] For example, the toxicity of Aroclor 1242 was studied with a hodgepodge of "one cat, 6 guinea pigs, 10 mice, 4 rabbits and 10 rats." Typically, at minimum, 15 to 20 animals would be tested in each species and there would be an equal number of age and sex matched control animals. It is not even possible to calculate the average toxic response for cats with only one cat test animal. Furthermore, many of the test animals were severely ill and suffering from infectious pneumonia which renders the entire study unusable.

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chronic throughout a person's entire life from various exposure pathways starting with exposures in the womb and during breast feeding. My analysis of Monsanto's toxicological studies is attached as Appendix C.

4.3.1.1. LD50

The overwhelming majority of Monsanto studies were "lethal dose 50" or LD50 studies. This is a very crude test to determine the lethal dose. An LD50 study, however, is not a toxicity study because it provides no information on the toxicity of a compound; it just establishes the lethal dose. These studies—also known as "dose-them-and-count-them" studies—use a single high dose to kill animals. The LD50 study is so named because laboratory animals are given one single high dose of a chemical and the number of animals that die within 14 days is then counted; that is the end of the study. The LD50 is then calculated by determining the chemical dose that killed 50% of the animals. No cause of death is determined; no pathology is conducted; and there is no urine analysis, no blood analysis, or any other examination on any organ system.

These studies provide no toxicity information and are only directly used by toxicologists in cases of suicides or accidental overdose. The lethal dose is also used to design a dosing regimen for chronic toxicity testing. However, Monsanto clearly did not use the LD50 information for those studies, since they did not produce any chronic toxicity study until 1970. It is unclear how, if at all, Monsanto used this information.

The LD50 study provides such limited information that the Pharmaceutical Manufacturers' Association recommended that the traditional LD50 test be *banned* because too many laboratory animals are killed for studies that yield little or no toxicity information Lebeau (1983).[52] Instead a "range find" test is substituted to delineate an approximate lethal dose with just a few animals.

4.3.1.2. Subchronic Rodent Studies

Subchronic rodent studies are usually 90-day studies and are useful for evaluating relatively short-term exposures, either in the workplace or to the general public. Like the LD50 studies, they are not relevant to toxic effects in members of the general public. Based on my review I

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could find no subchronic PCB Aroclor Monsanto study before 1971 and that study was on a chicken—a nonrodent species.

4.4. Throughout the 1940s-1960s, Monsanto misled customers and the public about PCB toxicity and the adequacy of its testing.

Throughout the 1940s–1960s, Monsanto appears to have misled many of its customers about the toxicity of PCBs. Moreover, while Monsanto was warning the chemical industry that toxicity studies should be performed on newly developed compounds, Monsanto did not perform any toxicity studies on PCBs, despite manufacturing hundreds of millions of pounds of the chemical.

In 1947, for example, Monsanto highlighted a recent address from Dr. Kelly (Monsanto’s Physician; WASHARCH00015) to the American Public Health Association (APHA).[53] In this address, Dr. Kelly focused on the challenges the industrial chemical field faced with regard to making sure “toxicological investigations” were “keep apace because it is broadening too rapidly.” He stated:

Although many new products are being developed by manufactures, the problem is to make certain that no new chemical is used in a manner in which systemic toxicity or skin irritation might result either in workers making the product or in consumers.

While Dr. Kelly specifically urged the chemical industry to ensure that “no new chemical is used in a manner in which systemic toxicity” might result “in consumers,” Monsanto itself did not follow Dr. Kelly’s advice regarding PCBs. Additionally, Dr. Kelly stated:

every new textile chemical developed by Monsanto is subjected to a laboratory study for such reactions culminating in patch testing on 200 human subjects. In plastics, animal experimentation involving, in some cases, two-year feeding tests must be made before they can be marketed. Some substances are so innocuous that they can be used in any application, while the use of others must be more limited.

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This statement is important for two reasons. First, it shows that Monsanto not only had the capability to conduct chronic 2-year animal studies but that it was actually conducting chronic animal studies as early as 1947 for other compounds it was producing. Second, the only way to determine if a compound is “innocuous” is to run toxicity tests to prove it. But Monsanto’s very first chronic animal study would have shown chronic PCBs exposures were not innocuous—but rather, were toxic and carcinogenic.

Another example of Monsanto providing misleading toxicity information is a 1950 response letter to Dr. Spolyar (Director of the Division of Industrial Hygiene, Indiana State Board of Health), who had written to Dr. Kelly asking for basic toxicity information on Aroclors. Dr. Kelly responded:[26]

The toxicology of Aroclors is somewhat confused. The experimental work done by Dr. Drinker at Harvard about 12 years ago, and was done in connection with chlorinated naphthalene, chlorinated diphenyl, and chlorinated diphenyl high boiler. Both of these last two are Aroclors. In the particular work at Harvard, Dr. Drinker found that Aroclor 1268, which means diphenyl chlorinated to 68%, was of low toxicity. The confusion existed in his findings that Aroclor 1254 which is the diphenyl chlorinated to only 54%, was considerably toxic on inhalation. We did not supply him with this material, and I was never convinced that some error might not have been made in the sample.

There are several misleading statements in Dr. Kelly’s letter. First, he stated, “We (Monsanto) did not supply him [Dr. Drinker] with this material” (referring to PCBs). While that may be true, Dr. Kelly knew that Dr. Drinker was testing Monsanto’s PCBs since it produced *all* PCBs in the United States. Second, it shows that, as late as 1950, Monsanto itself was unsure of Aroclor’s toxicity yet took no steps to conduct toxicity testing itself to deal with this uncertainty. As I will discuss below, dozens of studies were conducted by 1950 to evaluate the toxicity of DDT, and Monsanto could have addressed this “uncertainty” regarding PCBs by simply following the exact same scientific protocols used in 1945–1950 to investigate DDT. If Monsanto believed Dr. Drinker’s PCB study findings in 1937 were corrupted, flawed, or uncertain, Monsanto could have independently conducted its own PCB toxicity studies by 1950, when Dr. Kelly sent this

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letter. Third, although the Miller study provided unequivocal findings of PCB toxicity years earlier--in 1944--Dr. Kelly failed to offer that information or even provide a reference to Miller's study.

Even the steps Monsanto took to protect its workers seem to have been belated. While Miller (1944) showed toxicity linked to ingestion of PCBs, Monsanto did not warn its workers until a decade later that they should not ingest PCBs; Mr. Garrett wrote in a 1955 internal memo (MONS093616) that the Medical Department warned that eating contaminated food could lead to "serious difficulties:"[54]

It has long been the opinion of the Medical Department that eating in the process departments is a potentially hazardous procedure that could lead to serious difficulties. While the Aroclors are not particularly hazardous from our own experiences, this is a difficult problem to define because early literature work claimed that chlorinated biphenyls were quite toxic materials by ingestion or inhalation. In any case where a workman claimed physical harm from any contaminated food, it would be extremely difficult on the basis of past literature reports to counter such claims.

In 1963, another customer requested toxicity information about Aroclors. Dr. Kelly's response letter (PCB-ARCHO736677) to Mr. Hempel regarding TK Products Inc. seems misleading:

Even though they don't ask for the toxicity, I think we should tell them that these compounds do not possess the long-term toxicity needed for the toxicological clearance and that such clearance probably only can be obtained by showing non-extraction.

It is not clear why Dr. Kelly would state that PCBs do not possess "long-term toxicity" when Monsanto had never conducted any long-term toxicity tests on any Aroclor; Monsanto did not even have *preliminary* chronic toxicity information until the early 1970s. However, Kelly stated just the opposite in a letter just 4 years later to Mr. Wilde. In his 1967 letter, Dr. Kelly summarized a conversation he had just had with Dave Wood in Brussels about the recently published 1966 Jensen study that suggested PCBs were likely a worldwide contaminant. In that

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letter, Kelly admitted there was no chronic toxicity information on PCBs as of 1967 (MONS 096495):[55]

The customers would like some reassurance on the toxicity of Aroclor (I explained to Dave that there just was no information available on the action of nanograms of Aroclor in the human body over a lifetime). There is no toxicological work going on at present in Sweden and it appears there is some likelihood that it will not be able to obtain funding and might not be done. Everybody over there is 100% convinced that what Jensen and Widmark found was Aroclor.

Dr. Kelly admitted that there were no chronic toxicity PCB studies at that point. This highlights the fact that, even though he stated in his 1947 address that 2-year lifetime studies were being conducted by Monsanto for other compounds, PCBs did not merit investigation.

4.5. Monsanto's studies conducted by Industrial Bio-Test Laboratories, Inc. (IBT) would not be held as reliable by a reasonable toxicologist.

Fifty-five of the studies funded by Monsanto were conducted by Industrial Bio-Test Laboratories, Inc. ("IBT"). To the extent they bear on the carcinogenicity of PCBs, those studies are suspect because the results diverge so significantly from other cancer studies conducted by independent scientists in the 1970s and 1980s. Further, the three IBT scientists who oversaw the Monsanto PCB cancer studies (Drs. Paul Wright, James Plank, and M.L. Keplinger), were indicted and convicted of mail fraud, wire fraud, and making false statements because they submitted to the FDA false results of studies they conducted for Monsanto and another client for other non-PCB chemicals (<https://www.courtlistener.com/opinion/460360/united-states-v-moreno-l-keplinger-paul-l-wright-and-james-b-plank>).[56] And Philip Smith, an assistant toxicologist with IBT beginning around 1971, admitted in trial testimony that IBT falsified data

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in long-term, chronic toxicity tests performed on rats using Aroclors 1242, 1254, and 1260. (WATER_PCB-00056547–56623).⁸

The IBT debacle is well known with the field of toxicology as most toxicologists receive training in ethics and professional responsibility. The IBT story involves hundreds of fraudulent studies that were submitted to U.S. regulatory agencies. For example, IBT produced 801 toxicity studies of pesticides,[56] and their reports were submitted to EPA to show that those pesticides were safe. Following the discovery of IBT's false data during the trial of the three IBT scientists, EPA conducted a re-review of the IBT reports and found that 594 of those studies were invalid (74%) because they contained false or fraudulent data or information.

Although the fraud conviction did not relate directly to Monsanto's PCB studies, the Monsanto studies did not undergo an independent analysis. Additionally, the EPA has shown a reluctance to rely on IBT's PCB studies given the "suspicion with which their data are regarded." EPA, Proposed Rule, Toxic Chemical Release Reporting; Community Right-To-Know, 52 FR 27226-01 (July 20, 1987).⁹

Furthermore, Monsanto pressured IBT to change conclusions of their Aroclor cancer studies. Starting in 1970, the IBT laboratory prepared and sent several draft reports to Monsanto that presented the number of tumors that were found after rats were exposed to Aroclor 1260, 1254, and 1242. They also stated their overall conclusions about how the Aroclors should be classified as to being either carcinogenic or noncarcinogenic. IBT originally classified the tested Aroclors as "slightly tumorigenic." After reviewing the draft reports, Monsanto requested that IBT alter the language to "does not appear to be carcinogenic" and IBT agreed. This is shown in a July 18, 1975 Monsanto Memo from Dr. Levinskas (Monsanto's Manager of Environmental Assessment and Toxicology) to Dr. Calandra (President of IBT) where Levinskas unilaterally altered the IBT conclusion. Whereas IBT stated in the draft report Aroclors were "slightly tumorigenic"

⁸ Note, Monsanto's Elmer Wheeler stated in a February 23, 1973 letter that the studies performed by IBT created data "which has led the government agencies to permit the continued but restricted use." MONS 092758.

⁹ The FDA also decided not to rely on IBT's studies, explaining that "doubt has been cast" on studies by IBT. FDA, Final Rule, Polychlorinated Biphenyls (PCBs); Reduction of Tolerances, 44 Fed Reg 38330 (June 29, 1979) at p. 3833.

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Monsanto misrepresented the carcinogenicity to “does not appear to be carcinogenic.” (MONS 093565):

Dear Joe:

The attached table [attached to the memo] summarizes a comparison of the 3 revised AROCLOR [sic] reports (1242, 1254, 1260).

In 2 instances, the previous conclusion of “slightly tumorigenic” was changed to “does not appear to be carcinogenic.” The latter phrase is preferable. [emphasis added]

It is highly unusual and irregular for a chemical company to unilaterally alter the findings or conclusions reached by their own experts or contract laboratories conducting toxicity tests on their products. If Monsanto had requested IBT to make a revision based on a technical or scientific issue, it would perhaps be understandable (depending on the reason). However, according to the memo, no scientific explanation was given for the change and Monsanto simply directed IBT to alter the report. In Monsanto’s view, their phrase was simply “preferable.”

Altering the IBT cancer classification of PCBs should not be considered a minor “tweak.” Rather, Monsanto changed the classification of PCBs from a carcinogen to a non-carcinogen. When chemicals undergo animal cancer testing, a two-step process is always followed. In the first step, a determination is made whether a chemical is a carcinogen or not. This is a yes-or-no determination. If a chemical is determined to be a carcinogen, then and only then, is the dose response relationship evaluated to determine its cancer causing potency. That is, a determination is made to evaluate its potency as a “slightly, moderately, or very potent carcinogen.” Instead of following this standard two-step process, Monsanto in the very first step concluded PCBs were not carcinogenic. Obviously, this precluded a further determination of the cancer potency in the second step.

Monsanto made these changes in classification despite the fact that all the Aroclors caused focal hyperplasia and tumors. Exhibit 19, which is presented in the Monsanto memo, shows the number of tumors that were detected in the IBT cancer tests. It also shows the changes they

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directed IBT to make, altering the classification of each Aroclor to read “does not appear to be carcinogenic:[51]

Exhibit 19. Tumors Detected in IBT Cancer Tests

<u>Product</u>	<u>Supplemental Report #1 (mailed)</u>	<u>Supplemental Report #2 (JCC delivered)</u>
<u>AROCLOR 1260</u>		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	3	7
range of test animal nos:		
p. 9	600 to 800	100 to 300
p. 10	1000 series	800 to 900
p. 11	70 to 100	10 to 40
p. 12	500 to 600	80 to 200
p. 13	600 to 700	200 to 300
p. 14	700 series	200 to 300
<u>AROCLOR 1254</u>		
conclusion	slightly tumorigenic	slightly tumorigenic
hepatomas	6	6
<u>AROCLOR 1242</u>		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	7	3
range of test animal nos.	as in report #2 for AROCLOR 1260	as in report #1 AROCLOR 1260

From the table, it is clear that the Aroclors produced hepatomas in each case. Despite this clear evidence of tumors, Monsanto chose to arbitrarily change the cancer classification.

I have also reviewed a trial transcript dated 10.28.1991 that presents testimony by Mr. Philip Smith pertaining to Monsanto’s IBT 1970 PCB chronic toxicity studies. Mr. Smith testified that he was an assistant toxicologist with IBT and actively participated in IBT’s PCB studies. Mr. Smith admitted that IBT falsified data, information, and conclusions in these studies.

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Mr. Smith first testified to participating in generating falsified rodent body weight. During any toxicological testing protocol, body weight is always carefully measured because it provides very important information about the overall health of rodents. Because necropsy examinations cannot be carried out during the 2-year period, body weight is the best and most insightful proxy data that provides a window into a rodent's health. Accordingly, it is critical to weigh the animals frequently to monitor their health as well as food and water intake. Mr. Smith testified that "a lot of the body weight data" was missing and he was instructed to take all the rodent weight data that the laboratory had amassed and graph it, and then his superior, Dr. Wright, made up false weights for the missing data. These false data were inserted into the final IBT PCB reports submitted to Monsanto.

Additionally, Mr. Smith testified that the PCB-dosed rats' survival rate was "[v]ery poor," and he estimated it was less than 10 percent or less. Furthermore, some of that data was never recorded in laboratory notes and false survival rates were entered into the final study. No necropsies were performed on the dead animals due to advanced decomposition, which precluded pathological examination or a determination of the cause of death. There was also no record of the dead animals entered into the laboratory records so it was as if the animal had never been in the study and according to Mr. Smith they just "disappeared."

Based on Mr. Smith's testimony, the Aroclor study results and conclusions lack veracity and should not be considered as probative evidence for any conclusions IBT and Monsanto reached regarding PCB carcinogenicity. Moreover, all Monsanto subsequent presentations, publications, communications that relied on the falsified IBT cancer study findings should be disregarded as unreliable.

Given the differences between the IBT studies and other published animal cancer studies, the history of fraudulent activity at IBT, and admissions that IBT falsified data during PCB toxicity studies, a reasonable toxicologist would not hold the IBT studies as reliable studies.

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5. EXECUTIVE SUMMARY

Based on common scientific knowledge established by the late 1800s and routinely utilized in the scientific community for decades thereafter, Monsanto had all necessary information on the physicochemical property of PCBs by as early as 1945, and no later than 1950, to predict that PCBs would bioaccumulate and biomagnify in animals and humans.

Well before Monsanto began producing PCBs, the scientific community predicted bioaccumulation of a chemical based on the oil-water partition coefficient. By 1945, empirical evidence from actual environmental exposures to DDT was published. These studies confirmed that highly lipophilic compounds bioaccumulated and biomagnified in the food chain. By at least 1945, Monsanto must have known that DDT and PCBs were nearly equal with regard to lipid solubility (and thus would similarly bioaccumulate & biomagnify) because Monsanto was manufacturing both DDT and PCBs in 1944. The company also must have known from published DDT studies that bioaccumulation and biomagnification of DDT were solely governed by the physicochemical property of lipid solubility. This fact was known throughout the chemical industry. In addition, Monsanto must have known that both DDT and PCBs, due to their similar chemical structures, were extremely stable compounds and would be equally resistant to degradation and, therefore, both would be highly persistent when released into the environment.

Based on the similar lipid solubilities of DDT and PCB, and the overwhelming empirical evidence that had amassed for DDT, it is my opinion that Monsanto could have predicted and correctly concluded that PCBs would bioaccumulate and biomagnify in fat tissues of all animals and humans to essentially the same magnitude reported for DDT studies published in 1945–1950. For these and other reasons stated in this report, Monsanto must have known by 1945–1950 that its PCBs posed a significant risk of environmental persistence, bioaccumulation, and biomagnification in animals and humans.

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6. MONSANTO MUST HAVE KNOWN THAT PCBS WOULD BIOACCUMULATE AND BIOMAGNIFY BASED ON LIPID SOLUBILITY.

In this section, I present evidence to support my opinion that Monsanto must have known during 1935–1950 and thereafter that its polychlorinated biphenyls (PCBs; Aroclors) would bioaccumulate in animals and man. In this report, I define bioaccumulation as a gradual increase in PCB body burden that results from the net between absorption of PCB into the body minus its elimination from the body. When rate of intake and absorption of PCBs into the body exceeds the rate of excretion from the body, PCBs bioaccumulate with continued exposure. The body burden is the net sum of PCBs measured in the body at a particular point in time. PCBs bioaccumulate primarily in fat (adipose) tissue and in fat-rich cell membranes because PCBs are highly fat- or lipid-soluble compounds.

This opinion is based a careful reconstruction of the state of the science in the late 1800s and early 1900s regarding the physicochemical property of lipid solubility. This property was known to be the sole property responsible for the absorption of fat-soluble chemical compounds like PCBs through cell membranes and, ultimately, their sequestration in fat-rich tissues and membranes. As I will detail in this section, the theory for this physiological phenomenon was first postulated in the late 1800s; with each passing year, experiments solidified it into a scientific “rule.” By the early 1900s, scientists were applying this rule to make predictions about the degree to which compounds would preferentially be absorbed into animals (based on the partitioning between oil and water). To reconstruct the chronological sequence of studies that ultimately led to scientists to predict bioabsorption of organic chemical compounds, I reviewed approximately 70 historical peer-reviewed studies starting in the mid-1880s through 1945. I also examined historical reviews recently published by experts in the field. These contemporary scientists have compiled histories consistent with the one I present in this report.

The scientific industry understood principles of bioaccumulation well before Monsanto began producing PCBs. Therefore, Monsanto must have known that PCBs would bioaccumulate from

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the time it began manufacturing PCBs. A summary of facts supporting this opinion is as follows:

- A. The lipid solubility of a chemical was an easy physiochemical parameter to measure in the laboratory and was the only physical measurement needed to predict uptake and bioaccumulation in aquatic and terrestrial animals.
- B. The lipid solubility of numerous and diverse organic chemical compounds was quantified in the laboratory by the *oil–water partition correlation coefficient*, which described the relative degree of partitioning of a compound between oil and water.
- C. The first use of the oil–water partition coefficient to predict and quantify bioaccumulation in animals occurred in the late 1800s.
- D. The partition coefficient was the predominant property governing bioaccumulation in laboratory animals in the late 1800s; it was identified as the sole physicochemical property governing drug effects and toxicity.
- E. Aquatic organisms were the first animals tested in the late 1800s to determine the oil–water partition coefficients.
- F. By the 1930s and 1940s, lipid solubility was the primary physical property used by scientists to make predictions and comparisons regarding bioaccumulation in biological systems.
- G. Monsanto must have known by 1929 (when Swann Research Company started production) that PCBs were highly lipid soluble because the company referred to them as *oils* in its original patent that was granted.
- H. Any independent, competent scientist in the 1930s would have predicted PCBs were bioaccumulative based solely on the knowledge that they were highly lipid soluble and, therefore, would accumulate in cell membranes and fat stores; no further chemical-specific information was needed to make this prediction.

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- I. Monsanto must have known in 1935 that PCBs were extremely stable compounds based on their chemical structure and the strong chlorine-bond, which was resistant to degradation; based on this stability, Monsanto could have predicted that PCBs would be extremely persistent in the environment.

The analysis I present in this section focuses specifically on the oil–water partition coefficient as the single physical property that was used through the year 1944 to make predictions regarding bioaccumulation. I reconstruct the time period of approximately 1944–1955 to show how scientists verified their earlier predictions based on lipid solubility and partition coefficients by conducting environmental studies based on empirical data that proved their early predictions. In this section, I focus on one of the most notorious bioaccumulative and biomagnifying chemical compounds first identified as a ubiquitous and worldwide contaminant: dichlorodiphenyl trichloroethane (DDT)—a product that Monsanto manufactured starting in 1944. In this report, I define biomagnification as the accumulation of organic compounds (e.g., PCB and DDT) by animals and humans from chemical intake that results in a body burden that is greater than the intake concentration. This describes the increase or magnification of the body burden at each trophic level moving up the food chain. Because humans sit at the apex of the food chain, the body burden will be highest in man.

I opine that Monsanto must have known by 1950 that PCBs bioaccumulate and biomagnify. A summary of facts supporting this opinion is as follows:

- A. The scientific community utilized the lipophilic property of organic chemical compounds to predict bioaccumulation in biological animals;
- B. DDT and PCBs were similar chemical compounds possessing high lipophilic properties;
- C. Empirical evidence had accumulated to prove DDT bioaccumulates in fat tissue and biomagnifies as it moved up each successive step in the food chain; and

- D. Based on the similar lipid solubility of PCBs and DDT and the empirical evidence that had amassed by 1950 proving that DDT bioaccumulated and biomagnified in the food chain, Monsanto must have known that PCBs would likewise bioaccumulate and biomagnify in animals and humans.

6.1. For over 130 Years, Lipid Solubility Has Been Key to Determining the Potential for Bioaccumulation.

This section presents evidence of the pivotal role that lipid solubility plays in predicting bioaccumulation. It is the sole physicochemical property determining the potential for bioaccumulation, and it has been used for more than 130 years to predict bioaccumulation in biological systems.

In the environment, lipid-soluble organic chemical compounds partition into the fat tissue of biological receptors—particularly those in aquatic environments. Once an organism bioaccumulates lipid-soluble compounds, those compounds are biomagnified when eaten by a predator in the next trophic level. Since humans occupy the apex position in the food web, we have the highest bioaccumulation and body burdens of lipophilic chemical compounds. Finally, pregnant mothers transfer lipophilic compounds across the placenta and continue to expose suckling newborns to high concentrations of lipophilic compounds, ultimately rendering young children the most-exposed group in this long bioaccumulative chain (based on body weight). Young children are truly the apex group.

Lipid-soluble (also called *fat-soluble* or *fat-loving*) compounds bioaccumulate because they enter cells through passive transport. Membranes of all biological systems are made up of a lipid bilayer. Once lipid-soluble compounds are absorbed into the body, they are transported in blood bound to lipoprotein carrier molecules and are then distributed to fat tissue, where they are stored. These physiological phenomena of absorption, distribution, and storage can be predicted, and the magnitude estimated simply based on the lipid solubility of a chemical compound.

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The solubility in lipid is compared to a chemical's solubility in water and was initially defined as the *oil–water partition coefficient* because scientists used olive oil and water (today, this is known as the *octanol–water partition coefficient* because the distribution is measured in the laboratory using octanol and water). While the nomenclature has changed over the 130 years since the concept was first defined, the principle has remained the same and has been used to predict the bioaccumulation in terrestrial and aquatic animals, as well as in humans. Accordingly, I will use all of these terms interchangeably in this report.

The oil–water partition coefficient (or, *partition coefficient*) is a fundamental physicochemical property of all chemicals. Some chemicals preferentially dissolve in water, while others preferentially dissolve in lipid. By measuring how a chemical partitions between oil and water, scientists can predict how a newly synthesized chemical will partition into membranes and fat compartments of the body versus the water compartments. Thus, the partition coefficient is one of the most fundamental and basic laboratory analyses that, together with the boiling point and vapor pressure, is measured for all newly synthesized industrial chemical compounds. In fact, the partitioning coefficient is a *required* chemical parameter that *must* be determined to comply with U.S. and E.U. regulations as I discuss below.

However, it is not always necessary to conduct an actual partitioning laboratory experiment if the compound is highly lipid soluble and virtually insoluble in water (like PCBs). It is only necessary to calculate the oil-water partitioning coefficient for compounds that are on the *margins* where a compound is miscible in both oil and water to some degree. That is, the measurement need only be conducted on those compounds when there is some uncertainty in how it precisely partition between oil and water. When a compound is extremely lipophilic, such a measurement need not be carried out to make predictions about its fate and transport in the environment.

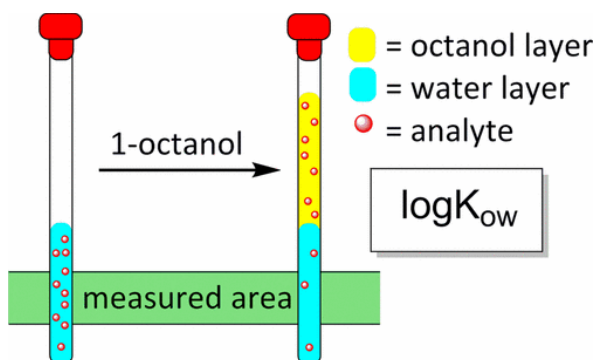
Based on Monsanto's chemical description of PCBs, it must have known that PCBs were not miscible in water and were highly lipophilic compounds. For example, in its 1944 sales brochure (MONS092683),[57] Monsanto stated that the solubility of water in Aroclor 1242 was 0.08% which (indicates that PCBs and water were essentially immiscible), while it was extremely

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miscible in many organic (lipophilic) industrial solvents like benzene. Thus, the oil-water partition coefficient for PCBs would be so high that an actual measurement was unnecessary.

The oil–water partition coefficient analysis is easy to measure and requires no special laboratory equipment. It is such a basic and fundamental physicochemical property that most undergraduate students taking a course in organic chemistry are taught how to conduct such analyses early in their academic training. It simply involves adding a test chemical compound to a vessel or test tube containing equal parts oil or octanol and water, mixing the solution, and then allowing the solution to equilibrate; the chemical concentration is then measured in each of the oil and water phases. The simple steps in this measurement are shown in Exhibit 20 below:

Exhibit 20. Oil–water Partition Coefficient Analysis



Source: Cumming and Rücker 2017.[58]

A chemical compound’s oil-water partition coefficient was measured in the late 1800s and early 1900s to characterize how numerous industrial organic solvents and drugs would accumulate in animals and the human body. By the early 1900s, this was known as the “Meyer-Overton Rule” (Perouansky, 2015).[59]

The importance of this single physical property cannot be overstated. It is now commonly used as the basis for the development of environmental regulations, as well as for human health and ecological risk assessments. For example, guidance for deriving the partition coefficient, which is known as the K_{ow} , was standardized by the U.S. National Bureau of Standards for the U.S.

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Environmental Protection Agency (EPA) more than 30 years ago so that diverse chemical compounds could be characterized in order to make predictions about their potential to bioaccumulate. Furthermore, numerical risk-based screening concentrations presented in regulatory guidance documents like the U.S. EPA's Soil Screening Levels tables were developed for the Superfund Program so they could be used to predict fate and transport of each organic compound at thousands of sites to track the movement of pollutants through the environment.[60], [61]

In addition, U.S. EPA's Office of Prevention, Pesticides and Toxic Substances' specific guidelines for testing pesticides emphasizes the importance of the partition coefficient:[62]

(ii) In the study of the environmental fate of organic chemicals, the octanol/water partition coefficient has become a key parameter. It has been shown to be correlated to water solubility, soil/sediment sorption coefficient, and bioconcentration. The importance of this property to SAR [structure activity relationships] is indicated by its discussion in the first chapter of Lyman, Reehl and Rosenblatt's (see paragraph (e)(11) of this guideline). These authors consider the measurement or estimation of the octanol/water partition coefficient to be the necessary first step [emphasis added] in assessing the fate of chemicals.

(iii) Of the three properties that can be estimated from K_{ow}, water solubility is the most important because it affects both the fate and transport of chemicals. For example, highly soluble chemicals become quickly distributed by the hydrologic cycle, have low sorption coefficients for soils and sediments, and tend to be more easily degraded by microorganisms. In addition, chemical transformation processes such as hydrolysis, direct photolysis, and indirect photolysis (oxidation) tend to occur more readily if a compound is soluble.

The critical importance of identifying fat-soluble compounds to predict bioaccumulation is not limited to the United States. The European Union's chemicals legislation, *Registration, Evaluation, Authorization and Restriction of Chemicals* (REACH), also requires the

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determination of the oil–water partition coefficient for every new chemical compound manufactured or imported in amounts ≥ 1 ton/year.[63] The European Union enacted REACH to address and prevent further environmental contamination. REACH puts the burden on the chemical industry to identify bioaccumulative industrial compounds, prove they are safe to use, and prove they will not cause widespread contamination.[64]

The REACH regulations state that the oil–water partition coefficient is the most important parameter to gauge absorption into biological systems; this parameter is known as Kow or, more specifically, the log of the Kow or log P.¹⁰

A Kow value of 1.0 indicates that a chemical compound is equally distributed oil and water (the log of Kow = 1 is zero). As the fat solubility increases for a group of chemical compounds, the Kow (or log P) increases concomitantly. The REACH defines a highly lipophilic compound that will bioaccumulate as log P = 4. A partitioning ratio or log P equal to 4 indicates that the compound will be soluble in octanol 10,000 greater than water (the ratio is 10,000:1). For comparison purposes, all Aroclors have log Kow values > 4.0 so they would be defined by REACH as highly bioaccumulating compounds that would be regulated. As shown in Exhibit 21 below, the range of PCB log Kow values increases with increasing chlorination of the mixture of PCB congeners from 4.7 to 6.8. This demonstrates that Monsanto's Aroclors have high bioaccumulation properties.

Exhibit 21. Aroclor Kow Values

Octanol-water partition coefficient	Aroclor 1221	Aroclor 1232	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
Log Kow	4.7	5.1	5.6	5.6	6.5	6.8

¹⁰ Log P is equal to log Kow and is sometimes used instead of Kow because it conveniently converts the oil-water partition values to a log scale. For example, log P = 0 is equal to 1. The log P values of 1–4 represent the Kow (oil water partition coefficient) equal to 10:1 (log P) to 10,000:1 (log P) parts oil:water.

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Source: ATSDR 2014.[65]

The Agency for Toxic Substances and Disease Registry (ATSDR) has also gathered information on the log Kow values for individual PCB congeners because PCBs constitute some of the most persistent chemicals that are routinely detected in human blood. Examples of log Kow values for five PCB congeners that have increasing degrees of chlorination are presented in Exhibit 22.

Exhibit 22. PCB Kow Values

Oil–water partition coefficient	PCB 77	PCB 138	PCB 153	PCB 169	PCB 180
Log Kow	6.04–6.63	6.50–7.44	8.35 6.72	7.408	6.70–7.21 (calc.)

Source: ATSDR 2014.[65]

The REACH regulations also note that, in addition to providing information on bioabsorption in the environment, the Kow is used to predict bioaccumulation that results from chronic exposures when elimination from the body is slow because of the chemical-specific *half-life*. That is, with each subsequent exposure (or continuous exposure over time), the lipophilic organic compound builds up in fat tissue and membranes because it is not be eliminated. When bioaccumulation exceeds elimination, body burden increases. The European Union concluded that the Kow threshold for bioaccumulation is 4.0:[63]

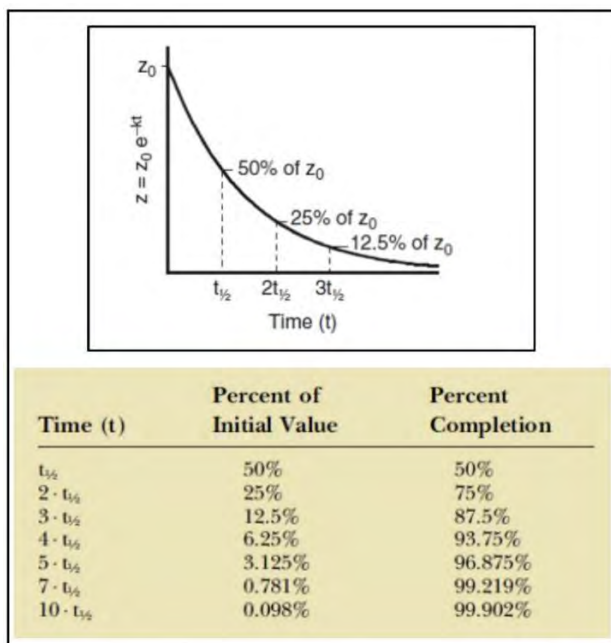
Lipophilic substances have the potential to accumulate within the body if the dosing interval is shorter than 4 times the whole body half-life. Although there is no direct correlation between the lipophilicity of a substance and its biological half-life, substances with high log P values tend to have longer half-lives unless their large volume of 10 distribution is counter-balanced by a high clearance. On this basis, there is the potential for highly lipophilic substances (log P > 4) to accumulate in individuals that are frequently exposed (e.g. daily at work) to that substance.

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REACH regulations focus on workers with their example of “daily at work” values utilized in chemical industry exposures. However, this issue is of critical importance to the general population when there are widespread environmental exposures that can lead to contamination of the food supply and the general population.

The concept of the chemical half-life is based on the time it takes for 50% of a chemical compound to be eliminated from the body (assuming exposure stopped at time zero and it follows a first-order elimination constant). This is illustrated in Exhibit 23.[66] As shown, it actually takes about 10 half-lives for the chemical to be *completely* eliminated from the body (assuming first order rate elimination kinetics). As a practical example, if a newborn child bioaccumulates a lipophilic organic chemical compound in the womb as a fetus, and then during breastfeeding, and that compound has a half-life of 5 years, it would take approximately 50 years for the entire dose to be eliminated from the body after the newborn has been weaned throughout its life (assuming that there is no further subsequent exposures).

Exhibit 23. It Takes About 10 Half-Lives To Eliminate Chemical From Body



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Source: Byers and Sarver 2009.[66]

The half-lives for different Aroclors and PCB congeners varies. For example, Exhibit 24 from ATSDR shows the “Apparent Half-lives” for individual PCB congeners:[67]

Exhibit 24. Apparent Half-lives of Aroclors and PCB congeners

Mixture	Elo et al. 1985	Hara 1985	Phillips et al. 1989	Steele et al. 1986*	Taylor and Lawrence 1992	Wolff and Schechter 1991*	Wolff et al. 1992*	Yakushiji et al. 1984	Yakushiji et al. 1984
Clophen A30	0.02								
Kanechlors									
300		5.1							
300/500		>15						0.67	7.1, 2.8*
Aroclors									
1242			2.6	2.0	1.8	0.9, +*			
1248							8.6		
1254			4.8		3.3		65		
1260				27.6	4.1	1.2, 0.5*			

Congener	Brown et al. 1989	Buhler et al. 1988	Chen et al. 1982**	Chen et al. 1982**	Luotamo et al. 1991*	Luotamo et al. 1991*	Ryan et al. 1993*	Wolff and Schechter 1991*	Wolff et al. 1992*	Yakushiji et al. 1984
153	12.4	0.93	47	26		**	3.8		**	27.5
105	3.9		0.58	0.51					**	
138	6-7	0.88	32	20			3.4		16.7	16.3
163	>20									
183						0.13			7.9*	
128			5.2	5.4					7.9*	
171						0.08			24	
156			*	*	*	*	4.0			
180		0.34	*	*	*	*	4.3			9.9
169							10.4			
170			47	71			3.9			

Source: ATSDR 2000.[67]

Based on these tables, it appears that as the lipid solubility of an Aroclor increases the half-life also increases. For example, both Philips et al. (1989) and Taylor and Lawrence (1992) show that Aroclor 1254 is eliminated from the body slower than Aroclor 1242. Aroclor 1254 is more lipid soluble than Aroclor 1242 based on their respective Log Kow values, which are 6.5 and 5.6.

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Independent from the regulations, the European Union has adopted testing procedures that are as restrictive as the official REACH regulations and has put into place industrywide procedures to predict which industrial chlorinated compounds have the potential to bioaccumulate. These testing procedures focus on lipid solubility as the property that is most important for screening of all new chemicals (as do the REACH regulations).

For example, Euro Chlor, an industry group representing chlor-alkali producers in the European Union and European Free Trade Association (EFTA) regions (which employ about 39,000 people at 69 manufacturing locations with almost 2,000,000 jobs in Europe) is intent on precluding both bioaccumulation and biomagnification in the food web:[68]

A particular concern attaches to substances that might 'biomagnify', such that the levels steadily increase in food webs from prey to predator (secondary poisoning) so the highest levels are found in animals at the top of the food chain (including humans). Complicating factors in the assessment of biomagnification are the increasing lipid content of higher organisms and changing lipid content of organisms over the year.

Euro Chlor recognizes that it is imperative to screen all newly synthesized compounds using “simple” laboratory analyses or computer modeling in order to predict which will bioaccumulate:

It is often possible, however, to 'screen' substances on the basis of some simple physical and chemical properties, or using computer modelling, to exclude the majority of substances from further consideration as they clearly do not have any potential to bioaccumulate, or to prioritise substances which appear to have the greatest potential to pose a risk.

One of the first analyses the group recommends is calculating the log Kow:

The octanol/water partition coefficient is an important bioaccumulation parameter that can be used as a surrogate measure to indicate or exclude the intrinsic potential of an organic substance to be taken up in fatty tissues.

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In summary, this section presents evidence of the pivotal role lipid solubility plays in predicting bioaccumulation. It is the sole physicochemical property determining the potential for bioaccumulation. As explained further in the next section, lipid solubility is not a new concept; it has been used for more than 130 years to predict bioaccumulation in biological systems. The importance of this single physical property cannot be overstated as it is largely the basis for the development of environmental regulations regarding lipid-soluble substances.

Monsanto must have known that PCBs were highly lipophilic from the time it began producing PCBs. PCBs were described in the early 1931 patent (originally filed in 1929) as “oils” by Swann Research Inc., indicating lipophilicity.[69] Later, when characterizing the physical properties of PCBs, Monsanto described them as being soluble in numerous organic solvents and as being virtually insoluble in water (MONS092683).[57] Monsanto’s own descriptions of its PCBs correctly defined them as highly lipid-soluble compounds, and PCBs would have been recognized as such in the 1930s by independent and competent scientists.

6.2. Chronological History 1880s-1945: Oil–Water Partition Coefficient and the Meyer-Overton Rule

This section addresses the question of whether Monsanto should have predicted or foreseen that lipid-soluble PCBs could bioaccumulate in biological systems if PCBs were released into the environment during the early period of their production (1935–1945). In order to answer this question, I have examined approximately 70 peer-reviewed studies published in 1850–1945 as a state-of-the-science framework from which to form my opinion.

I began by identifying the seminal studies that would have been used to define the concept of the oil–water partition coefficient. I then proceeded to establish the time period when the oil–water partition coefficient was used in diverse scientific disciplines as a predictive scientific tool to identify which new compounds were absorbed by animals and aquatic organisms. I ended my research on this topic in 1945, at which time it was no longer necessary for Monsanto and others in the chemical industry to rely solely on the partition coefficient because empirical evidence of bioaccumulation and biomagnification was now well established with numerous studies on DDT

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that were published during 1945–1950. At this point, it became necessary only to identify chemical compounds that had a lipid solubility similar to that of DDT. After these DDT studies were published, the only question remaining was how similar PCB was to DDT in terms of lipid solubility; if similar, Monsanto must have expected PCBs to bioaccumulate and biomagnify in similar ways. I also reviewed early Monsanto documents, patents, and peer-reviewed publications to analyze when the company first acknowledged that PCBs were lipid-soluble compounds.

My review revealed that the concept of organic substances partitioning between oil and water was a well-known physicochemical property of all chemicals as early as the 16th century. In fact, it seems as though the concept was developed from simple common sense and direct observation, almost akin to the discovery of gravity.

Diluting chemicals and substances in “like” solvents may have first been described by Paracelsus (Philippus Theophrastus Aureolus Bombastus von Hohenheim), who is regarded as the father of toxicology.[70] Kenndler and Maier (2018) traced the history of scientists and physicians first conceptualizing that idea that chemicals dissolve in solvents having similar properties.[71] Paracelsus is commonly thought to have noted that “likes dissolve likes,” which as most student chemists are taught comes from “similia similibus solventur.” *Likes dissolve likes* simply means that lipid-soluble compounds dissolve in lipids:

Such selections are often guided by the well-known rule-of-thumb “similia similibus solvuntur” concept, which may be understood as the three-word essence of the Rohrschneider’s polarity classification. It appears to have been formulated in analogy to the principle “similia similibus curantur”, attributed to Paracelsus, and “similia similibus curentur”, a motto of homoeopathy (for the source of the solubility rule see J.H. Hildebrand, R.L. Scott, The Solubility of Nonelectrolytes, ACS Monograph No. 17, Reinhold Publ. Corp., 1950).

The practical application of likes dissolves likes formed the basis for the separation of mixtures of chemicals based on their different solubilities (and is the basis of the field of chemical and gas

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chromatography) and is thought to have originated in the early 16th century. In establishing the date of the first laboratory procedure applying differential solubilities, Kenndler and Maier (2018) traced it to 1512:

A curiosity in the history of partition GC is the first traceable separation apparently based on gas liquid chromatography and described as early as in 1512, in the period between the Late Middle Ages and the early modern age, by Hieronymus Brunschwig (ca. 1450 - ca. 1512), in his book "Liber de arte Distillandi de Compositis. Das buch der waren kunst zu distilieren die Composita" (the title page of this book is shown in Figure 3)." (Gas Chromatography and Analysis of Binding Media of Museum Objects: A Historical Perspective. Substantia 2(2): 93-118. doi: 10.13128/substantia- 64, 2018.)

Kenndler and Maier described Brunschwig's experiment in which he used olive oil to separate ethanol (lipid-soluble) from water as follows:

Brunschwig, a German surgeon and botanist, describes a procedure in which the vapor from a mixture of alcohol and water was forced through a sponge moistened with olive oil, and was leading to the recovery of a small quantity of pure alcohol. Expressed in modern terminology, this technique represents a separation process based on frontal GLC, with the oil acting as a liquid stationary phase, the sponge as a porous supporting material, and the alcohol vapor as mobile phase.

They also presented a simple laboratory apparatus prepared by Tswett in his first experiment applying the concept of the partition coefficient to separate organic (lipid-soluble) compounds from solid matter in the early 1900s:

In his first publication from 1903 Tswett, a Russian botanist, described the successful separation of plant pigments. In his experiments, he applied a chlorophyll extract in ligroin (i.e. petroleum ether) at the top of a vertically arranged cylindrical glass tube (see Figure 2) filled with particles of a solid material with adsorptive abilities, and continued

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applying fresh ligroin. Tswett observed the formation of separated colored rings, which migrated through the tube and broadened during their migration.

Kenndler and Maier showed the chemical equipment Tswett used to dissolve the fat-loving chemicals (Exhibit 25).

Exhibit 25. Tswett's Chemical Equipment for Dissolving Lipid-Soluble Chemicals

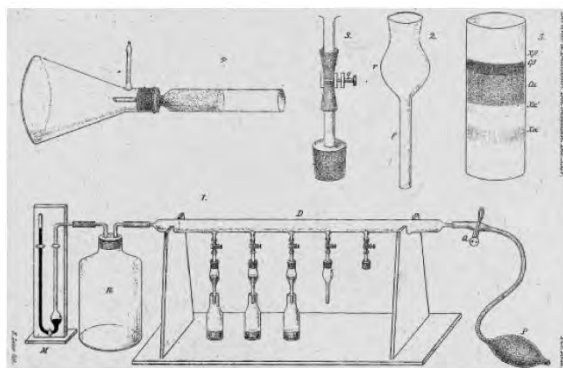


Figure 2. Tswett's device with four packed chromatographic glass columns. Drawing (1.): three columns filled with adsorbents for the separation of plant pigments. The columns had an inner diameter of 2-3 mm, and a length of 2-3 cm. Drawing (5.): Separated zones of 5 colored plant pigments (Chlorophylls and Xanthophylls) in a chromatographic packed column. From ref. [9] with permission.

Source: Kenndler and Maier 2018.[71]

The first investigations quantifying the oil–water partition coefficient focused on industrial organic solvents and organic compounds were reconstructed by Sangster (1997),[72] who described the key chronological milestones of research into this subject. He noted that the physicochemical property was first investigated as early as 1872 by Bertholet and was then independently investigated by Nernst in 1891.

The first oil-partition coefficient experiments on industrial compounds relied on symptoms of narcosis and toxicity as the endpoints. That is, to determine the degree of absorption and bioaccumulation into the bodies of terrestrial and aquatic animals, the toxic effects were observed, and the absorption was graded depending on the magnitude of the narcosis response.

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An increasing narcotic effect represents an increase in absorption. Organic compounds are still studied today by evaluating narcosis and the compound's lipid solubility. Narcosis follows a dose-response curve that is solely dependent on the lipid-solubility of organic compounds, whereby the chemical dissolves into the neuronal membrane and attenuates or blocks propagation of the electrical nerve signal in the central and peripheral nervous systems.

It should be emphasized that, although these organic chemicals were originally labeled *narcotic* compounds, these were actually industrial organic solvents that had recently been isolated from coal tar and petroleum products and used by chemical companies like Monsanto to dissolve chemical compounds, like PCBs (MONS092683).[57] These narcotic compounds included widely used solvents such as benzene, toluene, long chain alkenes, and hexane, which Monsanto identified as excellent solvents for PCBs.

In early oil–water partition experiments, symptoms and endpoints of narcosis included an animal's lethargy, stupor, drowsiness, delayed reactions, partial or total paralysis, and—with higher doses—death. It was easy to correlate an incremental decrease in motor movement with an increase in dose. A standardized scale could also be developed to compare different compounds with regard to the dose that results in complete paralysis.

The research in the late 1800s and early 1900s on narcotic compounds was not intended to study narcosis, but to categorize lipid-soluble solvents based on their ability to absorb into lipids based on the oil–water partition coefficient. Sangster described this work (1997):

Meyer (1899) and Overton (1899) independently reported that narcosis potency was governed not by water solubility but by partition coefficient. Meyer's conclusions were based on careful measurements of partition coefficients in his laboratory by Fritz Baum (1899) for a series of 11 anesthetics of diverse chemical structure using purified olive oil.

Meyer and Overton found that a compound's ability to produce narcosis was directly due its partition coefficient, or lipid solubility. Lipnick (1986) published numerous reviews of the historical work of Overton and his extensive and meticulous experiments in which he correlated

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solvent narcosis to the oil–water partition coefficient for more than 130 industrial compounds.[73]

Overton's early studies in the late 1800s are particularly relevant because his experimental design involved measuring the oil–water partition coefficient in an aquatic environment with tadpoles and small fish. Compounds that are highly lipid soluble preferentially partition into the fat-rich nervous systems of aquatic animals, causing paralysis. (Lipnick 1989).[74] Overton provided clear evidence of the fate of lipid-soluble compounds and showed they are absorbed by aquatic animals. As previously noted, many of the organic solvents Overton initially tested were chemicals that Monsanto would later show in 1944 (MONS092683)[57] were excellent solvents for PCBs, as described by Lipnick (1986):[73]

Overton employed algae and a wide variety of aquatic animals including tadpoles, daphnia, fish, crustaceans, bryozoa, and annelids to study toxicity at a constant blood plasma concentration. Most of the experiments which he reported in detail were conducted using tadpoles of the species Rana temporaria. The compounds tested included monohydric, dihydric, and polyhydric alcohols, aliphatic and aromatic hydrocarbons, nitriles, nitroparaffins, aldehydes, ketones, sulfones, esters of organic and mineral acids, various aromatic compounds, amines and alkaloids.

Overton's work not only established that the oil–water partition coefficient was the key property regarding absorption of individual organic compounds, but he also elucidated important toxicokinetic aspects such as the modulating effects of temperature on the time required for absorption of lipophilic compounds. Lipnick (1986) noted:[73]

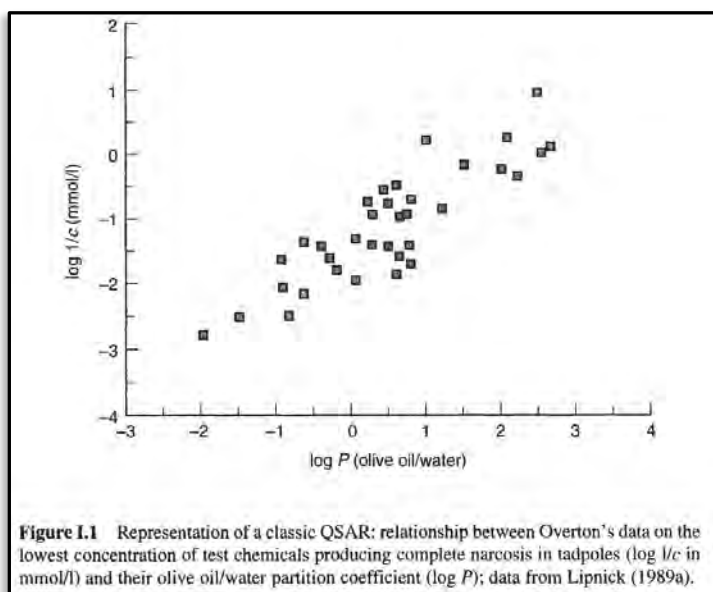
Overton found that within a homologous series, although the partition coefficient continues to increase with chain length, the absolute solubility in oil or a mixture of cholesterol and lecithin at room or blood temperatures decreases rapidly beyond a certain point in the series. For example, phenanthrene, which is readily soluble in olive oil and related substances at room temperature, is a narcotic, but anthracene, an isomer, is not soluble and does not show narcotic effects. Overton concluded that low water

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solubility alone will not limit narcotic toxicity, as in the case of phenanthrene which dissolves in about 300 000 to 400 000 parts of water, but produces narcosis at one part in 1500 000. For experiments conducted at this very low concentration, 36 h were required for complete narcosis to take place, which Overton accounted for based upon the slow rate of transport and accumulation of phenanthrene into the ganglia cells.

Lipnick reproduced Overton's results relating narcosis (bioabsorption) to the olive oil–water partition coefficient in Exhibit 26.[75]

Exhibit 26. Overton's Data on Test Chemicals Producing Complete Narcosis in Tadpoles



Source: Nendza 1998.[75]

Perouansky (2015) also published a retrospective on the scientific achievements of Overton's work and pointed out that Overton published numerous studies that were well known in the scientific community.[59]

Even at this early point, Overton linked the oil–water partition coefficient with the ability of an organic compound to be absorbed through the cell membrane and become embedded or stored in

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fat-rich substances. The fatty substances he highlighted were cholesterol, lecithin, and other oily substances that constitute all biological cell membranes, thus explaining why the lipid solubility property of organic compounds is the driving force controlling bioabsorption. Perouansky stated:

Overton published five papers between 1895 and 1900 reporting the results of his experiments on the permeability (referred to him, following contemporaneous terminology, as ‘osmotic properties’) of living plant and animal cells for biological and synthetic substances. In 1899 he expressed his ‘suspicion’ (note his avoidance of ‘hypothesis’) that cholesterin or cholesterin-like substances, possibly with lecithin and other oily substances, impregnated the boundary between cell protoplasm and the exterior. This became known as Overton’s lipoid theory or ‘Overton’s rule’, which states that the permeability coefficient of a solute is linearly related to its partition coefficient between oil and water. This work has since been celebrated as a foundation stone of membrane science.

Overton’s seminal work in the late 1800s was so important that he is now recognized as laying the foundation for the medical practice of anesthesiology. In his editorial in the *British Journal of Anaesthesia*, Perouansky specifically identified the oil–water partition experiments as a milestone in explaining absorption and bioaccumulation of organic lipophilic compounds:[59]

Hardly any discourse on anesthetic mechanisms avoids mention of the Meyer–Overton rule. Thanks to the eponymous rule, Charles Ernst Overton (1865–1933) enjoys together with Hans Horst Meyer (1853–1939) the highest name recognition where anesthetic mechanisms are concerned (Fig. 1). It may therefore come as a surprise, especially for clinicians, that the work underlying Overton’s contribution to the Meyer–Overton rule was merely a by-product of Overton’s principal body of scientific work; his lifelong interest in the movement of substances between the environment and the interior of living cells.

Perouansky went further to credit Overton’s work, which led to the Overton rule, as contributing to other scientific fields, including toxicology:

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Overton's work had far-reaching consequences well beyond anaesthesia. It became one of the foundation stones for the conceptualization of the boundary between cell protoplasm and its environment (known today as the cell membrane) and anticipated by several decades the understanding of impulse propagation in excitable membranes. Moreover, his contributions to structure–activity data, to toxicology, and to plant chemistry and genetics are also notable.

With contributions on the same oil–water partition coefficient phenomenon, another scientist—Hans H. Meyer (1853–1939)—was added to the Overton rule, which is now referred to as the Meyer-Overton rule.[74] This rule is based on the concept that predictions of bioaccumulation can be based solely on how organic industrial compounds partition between oil and water phases, as described by the laboratory measurement of the oil–water partition coefficient. Kurt H. Meyer (Hans Meyer's son) published a study in 1937 that summarized the “lipoid” mechanism, as follows:[76]

Any attempt to elucidate the mechanism of narcosis must take account of two well-known facts: firstly, that the same effect is produced by substances belonging to quite different classes of compounds, with a relatively high chemical inactivity as their only common characteristic; and, secondly, that many narcotics leave the body again completely unchanged, without having, on their part, effected any permanent change in it. This leads to the conclusion, first drawn by H. Meyer and Overton, that the action of narcotics depends on the formation of very loose compounds with certain cell constituents; in the opinion of both these workers these constituents were fat-like substances, the “lipoids.”

Meyer discussed how lipophilic compounds interact with lipids in the membrane:

There is hardly any other possibility than to take the limiting concentration and to determine, purely physically, the corresponding concentrations set up in various places: at the boundary surfaces, in the albumens, in the fats (triglycerides) and, finally, in the higher alcohols of the fatty series of the cholesterol type. Oleic alcohol was chosen as the model for substances of the latter class, it being the most closely related of all the readily

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available substances which might be considered for the purpose. The importance of this relationship cannot be overstated as it is the cornerstone of all fate and transport environmental studies.

Based on this relationship between the fat-rich membrane and lipid soluble compounds, Meyer stated that the empirical evidence was conclusive:

The deduction seems inevitable that such a constant concentration is set up also in the body lipoids, i.e. in the higher alcohols of the organism, and, further, that great biological significance must be attached to this rule. The experimental observation may be formulated as follows: Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipoids of the cell (or, to be more precise in the lipid alcohols of the cell substance) This concentration depends on the nature of the animal or cell, but is independent of the narcotic. The above statement seems to me to reproduce best the true nature of the Meyer–Overton lipoid theory: it is not really a theory which explains the mechanism of narcosis but rather the expression of an experimentally observed regularity, a rule of which every theory must take account.

This rule was well-established and used in many scientific disciplines to make predictions about the absorption of lipophilic compounds into terrestrial and aquatic animals by the turn of the 20th century—some 35 years before Monsanto started PCB production.

A competent, independent, academic or industrial scientist working in the early 1900s would have been knowledgeable of the Meyer–Overton rule and would have predicted—on the basis of knowing how lipid-soluble PCBs were—that PCBs were readily absorbed by environmental terrestrial and aquatic animals. A scientist could make such a prediction by knowing that PCBs were extremely lipophilic and were insoluble in water, even in the absence of knowing the specific oil–water partition measured value. As previously noted, determining the oil water partition coefficient of different Aroclors would have been extremely easy and could have been completed in a very short period of time.

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By the 1930s, the oil–water partition coefficient was routinely used as the primary tool to investigate the absorption of many different organic industrial compounds. Partition measurements were being used by pharmacologists and toxicologists to predict the absorption of different compounds into fat tissues of biological receptors for the purpose of developing drugs such as anesthetics. The potency of the effect, as well as the toxicity, could then be assessed simply based on a candidate compound being lipophilic. For example, Leake and Chen (1930) used the partition coefficient in pharmacology experiments to identify candidate anesthetic compounds from a family of structurally similar compounds (homologous series).[77] They predicted that increasing the carbon length would increase fat solubility, which would, in turn, increase absorption and ultimately increase toxicity:

From a general consideration of the chemo-pharmacological properties of di-ethyl ether and ethylene, especially in regard to their marked anesthetic power and relatively low toxicity, it seemed possible to predict that compounds combining the chemical characteristics of each would be interesting general anesthetic agents. This prediction might be made more specific by further reference to the theory of the relationship between chemical constitution and pharmacological action. In certain homologous series of absorbable aliphatic compounds (as the monohydric alcohols) toxicity increases (without a comparable increase in desired activity), in proportion to the number of carbon atoms in the straight carbon chain.

Exhibit 27 shows the results of the partition coefficient analyses conducted by Leake and Chen for six compounds. This clearly demonstrates that Monsanto could have rapidly and very easily characterized the oil–water partition coefficient for all Aroclor compounds.

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Exhibit 27. Leake and Chen: Partition Coefficient Analyses for Six Compounds

Substance	Formula	Molecular Weight	Boiling Point	Partition Coefficient, Oil : Water, at 20°C.
Di-ethyl ether	$\begin{array}{c} \text{CH}_3-\text{CH}_2 \\ \text{CH}_3-\text{CH}_2 \end{array} \rangle_0$	74	34.5°C.	2.3 ± 0.1
Vinyl-ethyl ether	$\begin{array}{c} \text{CH}_2=\text{CH} \\ \text{CH}_3-\text{CH}_2 \end{array} \rangle_0$	72	34-36°C.	0.5 ± 0.1
Di-vinyl ether	$\begin{array}{c} \text{CH}_2=\text{CH} \\ \text{CH}_2=\text{CH} \end{array} \rangle_0$	70	36-39°C.	2.5 ± 0.2
Allyl-ethyl ether	$\begin{array}{c} \text{CH}_2=\text{CH}-\text{CH}_2 \\ \text{CH}_3-\text{CH}_2 \end{array} \rangle_0$	86	68-74°C.	2.0 †
Isopropenyl-ethyl ether	$\begin{array}{c} \text{CH}_2=\text{C} \begin{array}{l} \nearrow \text{CH}_3 \\ \searrow \end{array} \\ \text{CH}_3-\text{CH}_2 \end{array} \rangle_0$	86	59-63°C.	0.61 ± 0.1
Di-allyl ether	$\begin{array}{c} \text{CH}_2=\text{CH}-\text{CH}_2 \\ \text{CH}_2=\text{CH}-\text{CH}_2 \end{array} \rangle_0$	98	92-98°C.	2.0 †

Source: Leake and Chen 1930.[77]

Hans Meyer's 1937 study extended the previous investigations on the importance of the oil–water partition coefficient in making predictions about bioaccumulation.[76] He showed that compounds with quite different chemical structures, but similar oil–water partition coefficients, are similarly absorbed.

A year after Meyer published his work, chemical industry scientists involved in the production of chlorinated compounds at chemical companies were using oil–water partition coefficients to classify industrial chemicals. For example, Ferguson (1938), who was a toxicologist at Castner-Kellner Alkali Company (which, like Monsanto, produced chlorinated organic compounds) published a treatise on the mechanisms of toxicity, stating [78]

A number of investigations have been published in which attempts are made to correlate the chemical or physical properties of substances with the intensity of their toxic action.

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Ferguson noted that, by this time, it was clear the physicochemical oil–water partition coefficient property governed absorption across the fat rich membrane and bioaccumulation for diverse lipophilic chemicals. He, like Meyer,[76] showed that diverse substances with the same lipid solubility will be absorbed similarly:[78]

The great influence of phase distribution relationships in determining the values of physiologically active concentrations if of course recognized in the Meyer-Overton lipid theory of narcosis. In the later form of this theory adopted by K. H. Meyer (Meyer and Hemmi 1935), it is assumed that isonarcotic effects are produced by the most diverse substances when their molar concentrations in the cell lipoids are identical.

He also noted that other studies were being published to correlate their physical properties with their toxic action.

A number of investigations have been published in which attempts are made to correlate the chemical or physical properties of substances with the intensity of their toxic action.

Ferguson was interested in extending Meyer’s lipid studies to correlate other chemical and physical properties of industrial chemicals and develop a rule for classification. Clearly, the oil–water partition coefficient properties of organic compounds was extending to toxicology and the chemical industry solely based on the property of lipid solubility.

By 1943, occupational physicians were warning their colleagues not to ignore the physical properties of industrial compounds with regard to the lipid solubility. For example, Dr. Goldblatt, of Imperial Chemical Industries (a large British industrial chemical company), delivered a lecture to the Association of Industrial Medical Officers in October of 1943 warning that lipid-soluble compounds could be absorbed into the body and pose a health threat to workers.[79] He stated:

The purpose of this paper is to draw the attention of medical officers in industry who are responsible for the health of workers engaged in operations involving the use or

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manufacture of toxic materials, to the importance of a measure of fundamental or elementary knowledge of the measures that must be taken to discover the dangerous properties of such materials.

Goldblatt urged his fellow physicians to focus on the physical properties of the diverse industrial compounds in order to identify those compounds with high lipoid solubility because they are absorbed through the skin, which can produce toxic effects:

In the vast field of organic compounds, there is a tendency to ignore purely physical properties, particularly when dealing with solids. I always look with suspicion at materials of low melting point and high or considerable lipoid solubility if in association with toxic radicles. These are the compounds which more or less readily penetrate the skin. In general, these compounds show little, if any, solubility in water.

Notably, Goldblatt expressed concern that lipophilic compounds pose a specific risk relating to lipid solubility. The emphasis had shifted from the toxic effects on the skin itself (like chloracne) to the bioabsorption through the skin that could lead to bioaccumulation in the body. That is, skin was not the target but was a route of bioabsorption and entry into the bloodstream, where the chemical could then attack target organs:

No discussion of industrial hazards can overlook reference to the skin. As an industrial route of entry of toxic products into the organism, the skin is second only to the lungs. Reference has been made to the rough general criteria of skin absorbability—viz. low melting point, lipoid solubility or miscibility, fat solvents.

By 1944, the oil–water partition coefficient was used as the basis for classifying chemical toxicity in industrial medicine and hygiene programs. For example, Lazarev (Lipnick and Filov 1992) used this sole physicochemical property to classify lipid-soluble organic compounds that were bioaccumulative and could cause toxic effects in workers.[80] Recognizing that many toxic industrial compounds were lipid soluble, Lazarev developed a framework based on the oil–water partition coefficient in a series of industrial hygiene studies in which he calculated the Kow for

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each compound. Lipnick and Filov noted that Lazarev called lipophilic compounds “nonelectrolytes” (they have limited solubility in water and are not charged molecules) and published a compendium of his work:

In his 1944 monograph Neelektrolity’ (Nonelectrolytes) (Fig. 1), Russian scientist Nikolai Vasilyevich Lazarev proposed a system for the biological, physical and chemical characterization of nonelectrolytes, using the logarithm of the olive oil/water partition coefficient (log Koil/water) as a primary measure of classification. This system provided a framework for developing a systematic approach to toxicology that was needed to set industrial hygiene standards for workplace exposure to organic chemicals in the Soviet Union.

Lipnick and Filov prepared a table from Lazarev’s work that shows numerous toxic effects are associated with an increase in the lipid solubility (partition coefficient) (Exhibit 28). It is particularly noteworthy that, as demonstrated by the previous studies by Overton and Meyer, scientists knew at this point in time that, with an increase in the partition coefficient, lipid-soluble chemicals bioaccumulate in both aquatic receptors and humans. That is, lipid-soluble industrial compounds could be predicted to accumulate in environmental and human receptors as they partitioned into fat-rich organs.

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Exhibit 28. Lazarev's Increasing Partition Coefficient Correlations

Table 1. Correlations of Lazarev with increasing partition coefficient or decreasing water solubility. (Adapted from [23].)

Effect	Subject
Increase in degree of irritancy of organic liquids	Skin
Increase in degree of reversible aggregation of liquid particles	Coacervate emulsion (phospholipid and oleate)
Decrease in concentration needed to produce a 6 % reduction in staining	Fixed frog gastrocnemius
Decrease in concentration needed	<i>In vitro</i> hemolysis
Decrease in concentration required	50 % Reduction of bird erythrocyte respiration
Decrease in concentration	Arrest of isolated frog heart
Decrease in minimum concentration	Contraction changes in isolated segments from heart ventricle
Decrease in concentration	Paralyzing action on isolated rabbit intestine
Decrease in concentration	Narcosis in tadpoles and small fish
Decrease in concentration in blood of mammals	Change in reflex time, narcosis, respiratory failure, or death
Decrease in blood concentration	Respiratory failure in frog
Decrease in concentration	Irritation of the eye or tongue
Decrease in concentration	Anesthesia via intradermal administration

Source: Lipnick and Filov 1992.[80]

Lipnick and Filov noted that Lazarev's industrial hygiene study built on the historical work started by the Meyer and Overton studies more than four decades earlier. Lazarev recognized the overwhelming complexity of evaluating each of the vast number and chemically diverse industrial chemicals to characterize the myriad toxicokinetic parameters (absorption, distribution, metabolism, and excretion [ADME]). As this would have been a Herculean task, Lazarev simplified the analysis of industrial compounds by exclusively focusing on lipid solubility using the Know (Exhibit 29):

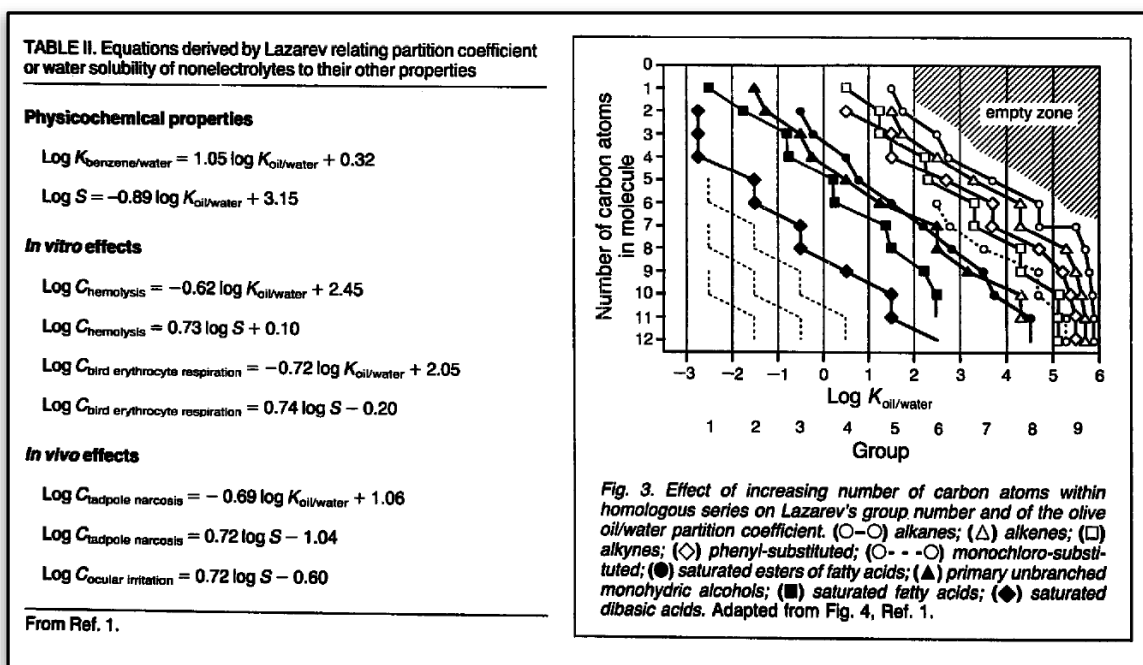
Given this complexity, he sought to derive regular relationships between chemical structure and physicochemical properties that could be used in relating chemical structure to biological activity. Although Lazarev considered studying various homologous series of compounds, he concluded that this approach was not practical due to the infinite number of such series. Instead, he chose as his starting point Richet's 1893 report of an inverse relationship between water solubility and narcotic effect on small

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fish, and the broader and more precise independent studies of Meyer and Overton relating partition coefficient to narcotic potency.

As noted in the previous discussions, this is the identical scientific approach that is still used today by U.S. and E.U. regulators to predict which industrial organic compounds will bioaccumulate in order to prevent worldwide pollution from organic compounds such as PCBs, which were historically released into the environment in massive quantities.

Exhibit 29. Lazarev's Kow Equations: Physicochemical Properties, In Vitro Effects, and In Vivo Effects



Source: Lipnick and Filov 1992.[80]

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6.3. Monsanto Must Have Known that PCBs Were Highly Lipophilic Oils, and Would Bioaccumulate, as Early as 1929

This section provides evidence that Monsanto must have known PCBs were lipid soluble the entire time it manufactured PCBs, such that Monsanto must have known that PCBs would bioaccumulate.

PCBs were initially produced by the Swann Research, Inc., starting in 1929, when a patent application for producing an “insulating di-electric liquid” adapted “to be used as a filling material for oil immersed transformers” was submitted by C. McCullough, et al., of the Swann company.[69] From this very quote, Swann (later acquired by Monsanto) knew PCBs were lipid soluble and even labeled them “oils” in the patent application.

As its patent application (Exhibit 30), Swann consistently referred to “chlorinated diphenyls” (as they were called then, rather than biphenyls or PCBs) as “oils:”

Exhibit 30. Excerpt from Swann Research, Inc., PCB Patent Application, 1929

The density of the oil may vary somewhat depending upon how far the chlorination is carried, for example it may vary between 1.22 and 1.28 at 25° C. A higher chlorine content will also increase the viscosity which we have found to vary between 40–50 seconds at 37.8° C.

While the proportions given above will give a satisfactory oil of the properties shown above, it should be realized that other proportions are possible and may be desirable for certain particular uses.

Source: <https://patents.google.com/patent/US1836180A/en>

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From this patent, it is clear that Swann/Monsanto knew PCBs were oils and were, therefore, lipophilic.

The next year (1930), Penning (who worked at Swann company) published a study detailing many of the physicochemical properties of PCBs.[81] One of the properties of these newly produced Aroclors that he emphasized was that they were lipid soluble and were miscible (dissolved) in “a large number of organic liquids” (as only lipophilic compounds are):

This mixture, being liquid through a wide temperature range, exhibits marked solvent properties, and is itself soluble in or miscible with a large number of organic liquids.

According to Penning, the Aroclor oils were stable (which led to their persistence because they do not undergo oxidation) and remained fluid oils that were thermoplastic (they do not change their physical state, which is an oil):

The Aroclor oils are non-drying; they undergo no appreciable oxidation or hardening on exposure to air. Similarly, the Aroclor resins are apparently permanently thermoplastic. They undergo no further condensation or hardening on repeated melting and cooling, so far as experiments have been carried.

Even in 1930, PCBs were known to be insoluble in water but soluble in a “wide range of other liquids, including practically all of the ordinary organic solvents,” as well as mineral and vegetable oils. This was not surprising, since all scientists had known since the 15th century that likes dissolve likes:

The Aroclors are insoluble in water; they are also insoluble in glycerol, and not readily soluble (particularly those of high chlorine content) in the lower alcohols, but they are soluble in a very wide range of other liquids, including practically all of the ordinary organic solvents, solvent mixtures, and mineral and vegetable oils.

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Exhibit 31 shows that Aroclors 1242 and 1254 were liquid oils at normal room temperature, while other terphenyls and higher chlorinated Aroclors were waxy resins (that become oils upon heating):

Exhibit 31. Physical Characteristics of Chlorinated Diphenyls

PROPERTY	TECHNICAL DIPHENYL	AROCLOR 1219	AROCLOR 1242	AROCLOR 1254	AROCLOR 1262	AROCLOR 1268	AROCLOR 2565	AROCLOR 4465
Appearance	Very light yellow crystals	Water-white liquid	Water-white liquid	Pale yellow liquid	Light yellow, waxy resin	Pale yellow, hard, crystalline mass	Black resin	Pale amber resin
Melting or softening point	68.6° C.	14° C.	Liquid at 0° C.	Pliable wax at 0° C.	Brittle resin at 0° C.	127–171° C.	78° C.	70° C.
Boiling point or distillation range	255.6°	278–295° C.	320–380° C.	360–400° C.	374–410° C.	395–415° C.	250–360° C. (10 mm.)	240–290° C. (9 mm.)
Specific gravity	1.007	1.1567 (25°/25° C.)	1.36 (65°/65° C.)	1.52 (65°/65° C.)	1.64 (65°/65° C.)	1.8 (65°/65° C.)	1.7 (25°/25° C.)	1.7 (25°/25° C.)
Viscosity, seconds Saybolt at 210° F.		30	34	46	96	Solid	Solid	Solid
Flash point	118–119° C.	127° C.	174–178° C.	210° C.	221° C.	241°	230°	257°
Flame point	139–143° C.	176° C.	224° C.	None below boiling	None below boiling	None up to 405° C.	None up to 405° C.	492° C.
Refractive index		1.6125	1.6248	1.6391	1.6493			

Source: Penning 1930.[81]

It is also interesting to note that, from the very beginning, PCBs were promoted as additives to surface coatings like varnishes, lacquers, and plastic resins because they were oily compounds and would, therefore, serve to prevent cracking, whereas coatings without the oily PCBs could become brittle. Penning described this as follows:

PROTECTIVE COATINGS—The protective-coating industries are greatly interested in Aroclor, and a large amount of work is being done in this line. Quick-drying tung oil varnishes have been made with both the viscous (Aroclor 1254) and the resinous (Aroclor 4465) Aroclors, and the solubility of the viscous products in linseed and tung oils indicates their use as plastic resins or gums for varnishes, especially of the short oil type where failure is due to cracking of a brittle resin present.

Penning also highlighted numerous other applications of PCBs that were being suggested by customers that could be used at reasonable prices:

MISCELLANEOUS USES—Printing inks, artificial leather, leather finishing, textile finishing—no attempt will be made to complete the list of multitudinous projects on which

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work is being done with the Aroclors. And when it is considered that these products represent only one of the many types of derivatives which may be made from diphenyl, one gets some idea of the enormous field opened by the production of this compound at a reasonable price.

Monsanto took advantage of the oil–water partition coefficient of PCBs in a 1944 patent application by Paul Benignus (a Monsanto employee).[82] In this patent, a new fungicide application was developed based on PCBs being insoluble in water but soluble in oils (meaning they would have a high oil–water partition coefficient). These oil–water emulsions (emulsions refer to a fine dispersion of minute droplets of oil suspended in water, as they are immiscible) were necessary because salts (which imparted the fumigant property) do not dissolve in PCBs, making the addition of water necessary to dissolve the salts.

One of the objects of the present invention is to provide a process whereby textiles, cordage, paper, wood and other cellulosic or part cellulosic materials may be impregnated with sufficient amount of relatively insoluble fungicidal agents in a single immersion to render the subsequently dried cellulosic material permanently and effectively resistant to the action of fungus and bacteria.

This fungicide emulsion was developed specifically for application to “textiles, cordage, paper, wood and other cellulosic or part cellulosic materials.” Uses of the treated fabrics and textiles were not specified, but it appears that any material used outside that could become wet and encourage fungal growth were potential materials for treatment. They were also materials that needed to be laundered or washed at some point with soap and water because Monsanto tested them under those conditions.

Ultimately, the goal of the PCB oil–water emulsion was clear: to make the coating “permanent” and water resistant. This new PCB-emulsion application would replace the water-soluble fumigant formulations used at the time that were removed with washing. Thus, Monsanto not only knew PCB had a very high oil–water partition property, but the company capitalized on this

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specific property of PCBs to develop this new PCB-emulsion application. Benignus emphasized these properties: [82]

However, subsequent wetting or laundering of the fabric thus treated tends to remove the fungicidal or bactericidal agent and thereby to reduce drastically the resistance of the fabric to fungi and bacteria.

The PCB-emulsion was prepared in a range of water phase to oil phase ratios, but a 1:1 ratio of oil–water was recommended:

The emulsion composition of the present invention may contain any desired proportions of water phase to oil phase in the range of 1:4 to 4:1. A desirable proportion is that of 50 parts of water and 50 parts of oil.

The proportion of PCBs in the emulsion could exceed 25% of the total volume:

The quantity of chlorinated diphenyl mixture which may be employed in the composition may be varied over a wide range, for example, from 3% or less to 25% or more.

Monsanto clearly identified the entire range of Aroclors that were amenable to this oil–water emulsion as it states that Aroclor 1242, 1254, and 1260 could be used:

The chlorinated diphenyls suitable as components of the composition of this invention are the mixtures of chlorinated diphenyls obtained by chlorinating diphenyl and which mixtures contain from 20–68% of chlorine.

It is interesting to note that Monsanto claimed that this new PCB-based oil–water emulsion would perform as advertised because the conducted tests to show the PCBs were not removed after the fabrics were laundered. In these tests, Monsanto treated “a cotton duck fabric” and washed it for 40 minutes at 100 degrees Celsius, and the PCB emulsion remained bound to the material and was not significantly altered:

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A cotton duck fabric was impregnated with the emulsion in a vessel equipped with squeeze rolls and known in the art as a padder. Following the impregnation, the fabric was air dried. A portion of the treated fabric was laundered for 40 minutes at 100° C with hot soap water, rinsed four times with water and air dried. The laundering procedure thus employed was that known as the standard cotton wash test of the American Association of textile Chemists and Colorists.

In addition to the patents, Monsanto also produced numerous sales brochures for its salesmen to share with potential customers, highlighting diverse physicochemical properties of PCBs, including that PCBs were highly soluble in a wide range of organic fat-soluble solvents, they were not soluble in water, and they were highly resistant to degradation. For example, a 1944 Monsanto Chemical Company “Salesmen’s Manual” for Aroclors (MONS092683) stated that they were mixtures of compounds based on “physical properties” rather than on “chemical composition.”[57]

DESCRIPTION AND PROPERTIES

The Aroclors are a series of chlorinated hydrocarbons based on biphenyl and terphenyl. They are not pure compounds but are mixtures of closely related chlorine substitution products manufactured essentially to a set of specifications based on physical properties rather than chemical composition.

Another page from this manual touts the number of organic solvents with which PCB was miscible (Exhibit 32). Being soluble in a wide variety of industrial organic solvents like benzene, toluene, and xylene created sales opportunities for PCBs. This highlights the fact that Monsanto clearly knew PCBs were lipid soluble because only lipophilic compounds are miscible with organic solvents. These were all organic solvents that were used industry-wide to dissolve oils, fats, and other lipophilic compounds the chemical industry was manufacturing.

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Exhibit 32. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Solubility of Aroclor 1268

MONSANTO CHEMICAL COMPANY		10-1-44
<u>SOLUBILITY</u>		
<u>Solvent</u>	<u>Aroclor 1268</u>	
	<u>Cold</u>	<u>Hot</u>
Acetone	I	I
Alcohol, Formula 3-A	I	I
Amyl Acetate	S	S
Amyl Alcohol	PS	S
Benzene	S	S
Butyl Acetate	S	S
N. Butyl Alcohol	I	PS
Carbitol	I	S
Carbon Disulfide	S	S
Cellosolve <i>Carbon Tetrachloride</i>	I <i>45</i>	S <i>70 50°C</i>
Chloroform	S	S
Di Butyl Phthalate	S	S
Ether	S	S
Ethyl Acetate	PS	PS
Ethyl Lactate	I	S
Ethylene Dichloride	S	S
40% Formaldehyde	I	I
Furfural	PS	PS
High Test Gasoline		
Glycerin	I	I
Kerosene	PS	S
Linseed Oil	I	S
Methyl Acetate	PS	PS
Mineral Spirits	<i>8</i>	<i>11 @ 50°C</i>
Paraffin		
Phenol 90%	PS	S
Pine Oil	S	S
Pyridine	S	S
Toluene	S	S
Tri Cresyl Phosphate	S	S
Tung Oil	I	S
Turpentine	<i>15</i>	<i>22 @ 50°C</i>
Xylene	<i>25</i>	<i>43 @ 50°C</i>
I = Insoluble PS = Partially Soluble S = Soluble		

Source: Monsanto Chemical Company's Salesmen's Manual 1944.[57]

PCBs were widely known in the scientific community to be lipid soluble. In his comprehensive toxicity study of Aroclor 1242, Miller emphasized that PCBs were insoluble in water but soluble in vegetable oils and "fat solvents":[17]

The chlorinated diphenyl used was viscous, almost water white, and clear at room temperature. It consisted of a mixture of isomers of diphenyl chlorinated in different positions and extent, with an approximate chlorine content of 42 percent and an

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approximate empirical formula of $C_{12}H_7Cl_3$. It was insoluble in water but soluble in mineral and vegetable oils, other chlorinated hydrocarbons, and fat solvents. Its specific gravity was 1.374 to 1.393.

7. MONSANTO KNEW IN 1935 THAT PCBS WERE STABLE AND PERSISTENT LIPOPHILIC COMPOUNDS.

In addition to its very high lipid solubility, Monsanto documents demonstrate an understanding of PCBs' stability. In fact, Monsanto referred to PCBs as stable compounds that resist degradation. This is the characteristic that lead to PCBs becoming a ubiquitous and worldwide environmental contaminant. Although the first study into the widespread environmental pollution of PCBs was triggered by Soren Jensen's (1966) work on this topic, Monsanto should have predicted and foreseen this result from the earliest chemical analyses of PCBs Because the chemical structure of PCBs had been known since its synthesis in the 1800s.[50]

As an example of Monsanto's knowledge of PCBs resistance to chemical breakdown (which was used in sales pitch to potential customers), it prepared a 1944 sales brochure (MONS092683) to tout the chemical stability of the PCB molecule. [57] Monsanto claimed in this brochure titled, "Salesmen's Manual: Aroclor Description and Properties" that one of the most "outstanding" physicochemical properties of Aroclors was its resistance to degradation from light, water, acids and alkalies, oxidation, and chemical action. The company was correct in 1944 to make such a statement. However, while the chemical stability of PCBs was widely recognized by Monsanto as a "virtue," serving as a sales pitch for Monsanto's Aroclors, the fact that they do not break down when released into the environment and can survive harsh environmental conditions cause the chemicals to be persistent in the environment.

In Monsanto's tests to determine PCBs' compatibility with different metals, Monsanto (MONS092683) showed that while there was some interaction with copper, it found no evidence of dechlorination from the biphenyl rings:[57]

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Toward Oxidation

When Aroclor 1254 is heated for 50 or 0 days at 150°C in the presence of oxygen and copper, there is likely to be some attack on the copper. Examination of Aroclor 1254 after that period of time will usually show the presence of soluble copper. This also occurs with mineral oil and other insulating liquids.

In general, even after severe oxidation conditions no evidence of chlorine splitting from the parent hydrocarbon has been found [emphasis added].

Likewise, PCBs were extremely resistant to degradation with high heat, as shown in Exhibit 33.

Exhibit 33. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Stability of Aroclor 1248

<u>STABILITY</u>			
<u>Toward Heat</u>			
Aroclor 1248 was heated to 650°F in stainless steel autoclave with the resulting changes indicated in the following tabulation:			
	<u>Time of Heating (Hours)</u>	<u>Temperature</u>	<u>Acidity mg. NaOH/gm. Aroclor 1248</u>
Original Sample	0	--	.0021
Autoclave #1	331	343°C. 650°F.	.0392
Autoclave #2	500	343°C. 650°F.	.0809
Autoclave #3	669	343°C. 650°F.	.0800
These results are interpreted as indicating very excellent stability for Aroclors under the conditions of test.			

Source: Monsanto Chemical Company's Salesmen's Manual 1944 (MONS092683).[57]

Monsanto summarized the stability of PCBs by noting four "valuable" properties, as seen in Exhibit 34.

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Exhibit 34. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Valuable Properties of Chlorinated Naphthalenes and Diphenyls

The chlorinated naphthalenes and diphenyls are valuable industrial products. Because of certain properties which they possess, we may briefly state these valuable properties as follows:

1. Resistance to water and alkali.
2. High insulating value. They possess high dielectric constant.
3. Thermo plasticity.
4. Quite stable chemically.
5. Flame resistant.

For these reasons, these substances possess much value industrially in the making of electric condensers, and in the insulation of wire and cable, etc.

Source: Monsanto Chemical Company's Salesmen's Manual 1944 (MONS092683).[57]

In another 1948 Monsanto Technical Bulletin (MONS 074287),[83] Monsanto extolled the fact that Aroclor 1254 was very persistent because it was resistant to degradation from "biological influences" and attacks by bacteria. This property is extremely important, because microbial degradation is one of the most efficient processes for degradation of industrial chemical compounds. In fact, many polluted sites rely on microbial degradation as a remedy selected for cleanup.

Statements that none of the known physical mechanisms for degrading chemicals would work on PCBs, and that PCBs do not undergo microbial degradation, indicate an understanding of PCBs' stability and persistence. From as early as 1948, Monsanto's documents extoll PCBs' resistance to microbial degradation:

VIII. ADVANTAGES OF USING AROCLOR 1254 IN COMBINATION WITH DOP (a coplasticizer)

1. *Depending on the plasticizer ratios used as indicated above, it is possible to save from \$1 to \$2 per cubic foot of plastic.*

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2. *Aroclor 1254 offers superior pigment grinding and pigment dispersing qualities in preparing the organosol.*
3. *The use of Aroclor 1254 in these plastics markedly reduces their susceptibility to burning.*
4. *Aroclor offers outstanding electrical properties and resistance to organism attack.*
5. *Aroclor offers toughness and tensile strength and in other respects the over-all qualities of the plastic such as “hand”, flexibility and gloss are maintained.*
6. *Aroclor 1254 resists attack by biological influences.*

Most organic compounds breakdown and are detoxified in the environment by microbial degradation. Not only were PCBs highly resistant to “microorganism attack” but Monsanto believed that PCBs could actually kill microorganisms (PCB-ARCH0232927). In a 1948 letter to Dr. Leake of the U.S. Department of Agriculture (MONS 1987737), Dr. Benignus stated that work had been ongoing to evaluate Aroclor 1242 as a pesticide (miticides, larvicides, and mosquito repellents):[84]

During a recent trip to Washington, we had opportunity to discuss with Dr. E.E. Knipling the work done with Aroclors at Orlando, Florida, as lousicides, miticides, larvicides and mosquito repellents given in the USDA Report E-733.

and

Although the biphenyl Aroclors, and especially the lower chlorinated members of the series are known to possess activity as lousicides, miticides, larvicides and show synergistic action on nicotine, these properties seem to diminish with higher chlorination...

In addition, Monsanto was in the process of determining the solubility of Aroclors in DDT and even provided PCBs to the Department of Agriculture so the agency could perform its own tests.

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In accordance with Dr. Knipling's suggestions, we are sending you without charge one gallon each of Aroclors 1221, 1232, 1242 and 1248 and also one gallon of MB-40. Our laboratory is scheduled to determine the solubility of DDT in the various Aroclors and also check the similar solubility in MB-40. It is our understanding that MB-40 will dissolve about 20 percent by weight of DDT. MB-40 is considered to be relatively non-phytotoxic.

In a 1950 Monsanto Technical Bulletin (PCB-ARCH-EXT0020686), Monsanto again highlighted the fact that Aroclors could kill soil microbes—the very microbes that were responsible for PCB degradation—even labeling them as “soil-poisons.”[85]

AROCLORS USED IN COMBINATION WITH SANTOPHEN* 20
(PENTACHLOROPHENOL TECHNICAL) IN THE PREPARATION OF WOOD-
TREATING FORMULATIONS AND SOIL-POISONS*

In addition to insecticidal properties, Monsanto must have conducted tests to ensure PCBs were stable in soil, since PCBs would not have commercial value as pesticides if they underwent environmental degradation:

Liquid Aroclors such as Aroclor 1242 are highly efficient soil-poisoning agents used to treat soil to protect wood against attack by termites.

In a 1953 technical bulletin (TOWOLDMON0037820), Monsanto promoted the use of Aroclors as pesticide “extenders” to be mixed with Lindane (a pesticide):[86]

Synergism, however, cannot be readily predicted and the possibility of synergism in this Aroclor-lindane mixture is at the present time being investigated by the Bureau of Entomology and Plant Quarantine.

Although the document primarily referred to Aroclor 5460 (which is a terphenyl), it does mention using Aroclors 1254, 1260, and 1268.

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In 1961, Monsanto explicitly promoted the fact that Aroclors were “just about the most unreactive materials ever synthesized” and resistant to degradation in an advertisement in *Chemical & Engineering News* (PCB-ARCH0232927).[87] The blaring heading stated:

*“THE UBIQUITOUS AROCLOR “GENIE” DOES IT AGAIN!
SECRET OF THE SORCERY?”*

Monsanto claimed that Aroclors were just about the most “unreactive materials ever synthesized.” According to Monsanto, they “stubbornly refuse to volatilize, oxidize, hydrolyze, harden, disintegrate, burn, condense, or corrode anything!”

8. MONSANTO MUST HAVE KNOWN BY 1945-1950 THAT PCBS BIOACCUMULATE AND BIOMAGNIFY.

This section will show that, by 1945-1950, Monsanto must have known that PCBs would bioaccumulate in the environment given 1) the chemical’s similarity to DDT and 2) knowledge in the scientific industry that DDT bioaccumulated and biomagnified in the food web.

Between 1945 and 1950, an explosion of peer-reviewed scientific studies provided definitive proof that a highly lipophilic and persistent chlorinated organic compound (DDT) would bioaccumulate and biomagnify in the food web. From the start, all DDT investigations singled out lipid solubility as the one property responsible for DDT bioaccumulation and biomagnification. By 1944, Monsanto was producing both DDT and PCBs;[88] both chemicals have very similar chemical structures and nearly the same lipid solubility. Based on my research, the entire scientific and regulatory community was keenly aware of DDT’s ability to bioaccumulate and biomagnify based on its lipid or fat solubility (Woodard 1945; Bishopp 1946).[89], [90] Given that PCBs have similar chemical structures and nearly identical lipid solubility, Monsanto must have known that PCBs would bioaccumulate and biomagnify if released into the environment. Given that PCBs have similar chemical structures and nearly

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identical lipid solubility, Monsanto must have known that PCBs would bioaccumulate and biomagnify if released into the environment.

As discussed in the previous sections, the lipid solubility of PCBs was the only physicochemical laboratory information that would have been necessary for Monsanto to predict the bioaccumulation of PCBs into animals and humans, and as discussed above, Monsanto must have been aware by 1935 that PCBs were lipid soluble.

Starting in 1944, new and empirical information was published in the major peer-reviewed scientific journals proving that a lipophilic compound would bioaccumulate and *biomagnify*. These studies analyzed DDT.

By about 1950, the amassed published studies left no doubt in the scientific and regulatory communities that DDT was highly bioaccumulative and biomagnified in the food web. Even the earliest studies proved this fact; by around 1946, when the question of bioaccumulation was definitively answered, attention focused on how far up and how fast DDT traveled up the food chain. With the alarming answer that DDT could easily biomagnify between species by 10- or 100-fold and very rapidly contaminate the entire food web, the questions very quickly moved to human exposures and health. The questions of whether DDT was absorbed through the placenta to expose the human fetus and whether it was secreted into breast milk were also answered in a quick succession of studies. Science is typically cautious, methodical, and slow, but the answers to all these questions regarding DDT were answered almost immediately in by 1950. Afterword, there were few remaining questions regarding bioavailability and biomagnification. Next scientific investigation turned to determining the toxic effects associated with the inexorably bioaccumulated DDT in humans and the U.S. food supply. In this section, I summarize the most salient aspects of the published research dealing with bioaccumulation and biomagnification during 1945–1950. Given the similarities between DDT and PCBs, the industry-wide knowledge of DDT bioaccumulating and biomagnifying, and the fact that Monsanto manufactured DDT, Monsanto must have known by 1945-1950 that PCBs would bioaccumulate and biomagnify if released into the environment.

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DDT was first synthesized in 1874, but its effectiveness as an insecticide was only discovered in 1939. Shortly thereafter, and particularly during World War II, chemical companies in the United States began producing massive quantities of DDT to control insects that were responsible for a wide variety of vector-borne diseases such as typhus and malaria in order to protect U.S. troops fighting abroad. After 1944, DDT production shifted to widespread commercial use, and massive amounts of DDT were intentionally released into the environment to kill insects. Although DDT was assumed to be safe during wartime exposure, the Department of Defense conducted no studies related to the impacts of DDT on the environment or food web, or any short-term or chronic toxicity studies. Determinations regarding the toxicity and safety of DDT were largely based on a few acute lethality studies. It was only after 1944-1945 when commercial production began in earnest for several chemical companies (as noted previously Monsanto's production began in 1944), that numerous scientific studies were launched. These studies focused on the impacts of DDT on the environment, environmental terrestrial and aquatic receptors, livestock, and the food supply, as well as human exposures.

Massive quantities of DDT were released into the environment from 1945 to 1972. EPA states:[91]

After 1945, agricultural and commercial usage of DDT became widespread in the U.S. The early popularity of DDT, a member of the chlorinated hydrocarbon group, was due to its reasonable cost, effectiveness, persistence, and versatility. During the 30 years prior to its cancellation, a total of approximately 1,350,000,000 pounds of DDT was used domestically.

Although it is widely assumed that Rachel Carson's book *Silent Spring* started the push to ban DDT, that effort started more than a decade before. In the late 1950s, regulatory action was initiated to limit environmental uses; by 1972, DDT was banned. The EPA provides a brief summary of DDT's historical use and ultimate ban:[92]

The U.S. Department of Agriculture, the federal agency with responsibility for regulating pesticides before the formation of the U.S. Environmental Protection Agency in 1970,

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began regulatory actions in the late 1950s and 1960s to prohibit many of DDT's uses because of mounting evidence of the pesticide's declining benefits and environmental and toxicological effects. The publication in 1962 of Rachel Carson's Silent Spring stimulated widespread public concern over the dangers of improper pesticide use and the need for better pesticide controls.

In 1972, EPA issued a cancellation order for DDT based on its adverse environmental effects, such as those to wildlife, as well as its potential human health risks. Since then, studies have continued, and a relationship between DDT exposure and reproductive effects in humans is suspected, based on studies in animals. In addition, some animals exposed to DDT in studies developed liver tumors. As a result, today, DDT is classified as a probable human carcinogen by U.S. and international authorities.

EPA provides a short chronological summary of the regulatory action milestones taken as early as 1957 to protect "aquatic areas:"

Initial Federal Regulatory Actions

The Federal Government has not been oblivious to the hazards of DDT use as is indicated by various Government studies and actions undertaken since the late 50s.

- 1. In 1957, as a matter of policy, the Forest Service, U.S. Department of Agriculture (USDA), prohibited the spraying of DDT in specified protective strips around aquatic areas on lands under its jurisdiction.*
- 2. In 1958, after having applied approximately 9-1/2 million pounds of the chemical in its Federal-State control programs since 1945, USDA began to phase out its use of DDT. They reduced spraying of DDT from 4.9 million acres in 1957 to just over 100,000 acres in 1967 and used persistent pesticides thereafter only in the absence of effective alternatives. The major uses of DDT by the Forest Service have been against the gypsy moth and the spruce budworm. The development of alternative pesticides such as*

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Zectran, which was in operation in 1966, contributed to further reduction in DDT use by the Department.

- 3. In 1964, the Secretary of the Interior issued a directive stating that the use of chlorinated hydrocarbons on Interior lands should be avoided unless no other substitutes were available. This regulatory measure, as well as others which followed, was reaffirmed and extended in June 1970, when the Secretary issued an order banning use of 16 types of pesticides, including DDT, on any lands or in any programs managed by the Department's bureaus and agencies.*
- 4. Between November 1967 and April 1969, USDA canceled DDT registrations for use against house flies and roaches, on foliage of more than 17 crops, in milk rooms, and on cabbage and lettuce.*
- 5. In August 1969, DDT usage was sharply reduced in certain areas of USDA's cooperative Federal-State pest control programs following a review of these programs in relation to environmental contamination.*
- 6. In November 1969, USDA initiated action to cancel all DDT registrations for use against pests of shade trees, aquatic areas, the house and garden and tobacco. USDA further announced its intention to discontinue all uses nonessential to human health and for which there were safe and effective substitutes.*
- 7. In August 1970, in another major action, USDA canceled Federal registrations of DDT products used as follows: (1) on 50 food crops, beef cattle, goats, sheep, swine, seasoned lumber, finished wood products and buildings; (2) around commercial, institutional, and industrial establishments including all nonfood areas in food processing plants and restaurants, and (3) on flowers and ornamental turf areas.*

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EPA highlights the fact that DDT was largely banned in 1972 because it was lipid soluble and bioaccumulated in animals and humans—the same reasons PCBs were banned just 5 years later.

DDT and PCB are very similar compounds. Because of their similar lipid solubilities, both chemicals are bioaccumulative and persist in the body for long periods of time. In fact, DDT and PCBs are still detected in blood samples today, even though both were banned approximately 50 and 40 years ago, respectively.[93]

In this section, I have reconstructed the historical state of the science of DDT research. My historical reconstruction begins in 1945, after Monsanto began producing DDT, and continues through about the next 5 years—to 1950—at which point an overwhelming cache of studies were published and available. It should be noted that after 1950, hundreds of DDT studies were published, but they only refined what scientists already knew about the chemical's bioaccumulation and biomagnification properties.

My initial query of published studies in the National Library of Medicine (PubMed) revealed an extensive database of peer-reviewed published works on DDT during 1945–1950. In just this 5-year period, 700–800 studies were published on numerous aspects of DDT. This is an extraordinary number of studies published over such a short period of time. This large collection studies indicates that: 1) the Department of Defense had not conducted many toxicity studies on DDT before 1945 and 2) the initial findings on the potential for bioaccumulation and toxicity in 1945 launched several new studies in many different directions. After vetting the larger database of DDT publications, I identified those that provided the clearest empirical evidence of contemporary knowledge.

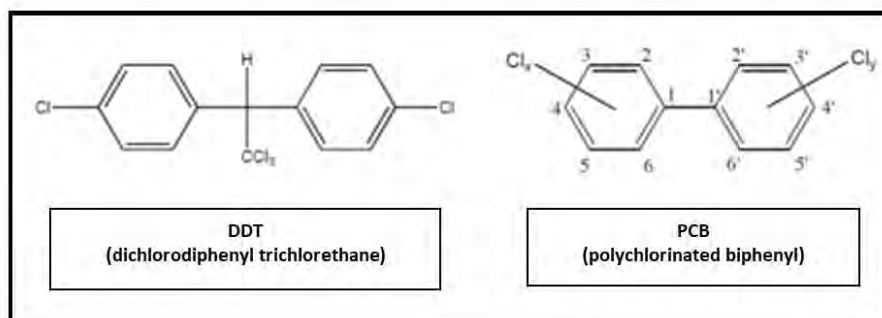
Given the similar chemical characteristics of DDT and PCBs, and the knowledge held by the scientific industry during 1945-1950, Monsanto must have known during that period that PCBs would bioaccumulate and biomagnify in people and animals if released into the environment.

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8.1. PCBs and DDT Share a Similar Chemical Structure.

As an insecticide, DDT was produced in a technical grade mixture comprising up to 14 similar chemical compounds, of which only 65–80% was the active ingredient, p,p'-DDT. As shown in Exhibit 35, DDT is a relatively simple organic chemical compound: two phenyl groups are attached to trichloroethane. The chemical structure of DDT is similar—but not identical—to that of PCB in that both contain phenyl rings.[67], [94]

Exhibit 35. Chemical Structures of DDT and PCB



Source: ATSDR 2000, 2002.[67], [94]

Both DDT (technical grade) and PCBs (as Aroclors) were complex mixtures of many closely related individual chemical compounds. Theoretically, it is possible to synthesize 45 dichlorodiphenyl trichloroethanes by virtue of different chlorine substitutions made on the two phenyl rings.[95] Likewise, 209 possible different individual PCB congeners can be synthesized, depending on the number and location of chlorine molecules on the biphenyl rings. Different Aroclor formulations were produced for different industrial uses; while each Aroclor mixture differs slightly, they all share physicochemical properties of being highly lipophilic, very stable, and virtually resistant to environmental degradation. Accordingly, these properties are the primary focus of this section of my report because they govern bioaccumulation, biomagnification, and environmental persistence.

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Both DDT and PCBs are highly lipophilic. Exhibit 36 shows that DDT and Aroclors 1242, 1254, and 1260 have very similar partition coefficients; thus, they are all similarly absorbed into biological systems.

Exhibit 36. Octanol-Water Partition Coefficients: Comparing DDT and Aroclor

Octanol-water partition coefficient	DDT	Aroclor 1242	Aroclor 1254	Aroclor 1260
Log Kow	6.9	5.6	6.5	6.8

Source: Sources: ATSDR 2002, 2014.[65], [96]

Monsanto, as a manufacturer of both DDT and PCBs, must have known about this similar characteristic of PCBs and DDT early on. Chiefly, because both compounds share the same physicochemical property of lipid solubility and dissolve in the same solvents.

In 1943, (a year before Monsanto started producing DDT), Haller and Busbey described the solubility of DDT as:[97]

practically insoluble in water, but is soluble in a wide variety of organic solvents, such as acetone, benzene, xylene, chloroform, carbon tetrachloride, vegetable oils, petroleum oils, and many others. Crude or unrefined kerosene can be used to prepare solutions containing 5 percent of DDT, but refined kerosenes require the addition of 10 to 20 percent of an auxiliary solvent. For this purpose, xylene, cyclohexanone, and alkylated naphthalenes have been used.

Monsanto sales brochures explained that PCBs were soluble in the very same organic solvents (MONS092683).[57] This common characteristic would have signaled a similar likelihood of bioaccumulation.

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8.2. State of the Science, 1945–1950

Insecticidal preparations containing DDT were first brought to the attention of the U.S. Department of Agriculture in October 1942 by the Geigy Co., Inc., New York, NY.[95] From the start, DDT proved to be a very effective insecticide. Once the effectiveness was proved, and DDT started to enjoy wide use in the United States, demand increased, and production soon exploded. Soon afterward, other chemical companies started their own DDT production. One of these companies was Monsanto, which produced DDT from 1944–1957.¹¹ According to Monsanto’s corporate representative, Monsanto was aware of the DDT literature during this time period.¹²

For insecticidal use, DDT was produced in a technical grade mixture comprising up to 14 similar chemical compounds, of which only 65–80% was the active ingredient, p,p’-DDT. As shown in **Error! Reference source not found.**, DDT is relatively simple organic chemical compound: two phenyl groups are attached to trichloroethane.

Early warnings about DDT use started in 1945–1946. DDT’s effectiveness in controlling disease transmitted by insects was widely hailed from the very start, but many scientists, public health officials and environmental agencies urged that only low volumes be used to prevent widespread environmental releases. This was because many early studies showed that DDT could kill both terrestrial animals and fish.[98], [99] Moreover, warnings were issued in 1946 (2 years after Monsanto started DDT production) that humans should not come into contact with the oil-DDT formulation because it was lipid soluble and would be readily absorbed through the skin. In a 1946 editorial in the *American Journal of Public Health*, [100] the American Public Health Association (APHA) stated that DDT is “definitely toxic to man and domestic animals” and that it should not be allowed to get into foods or “applied to the skin in an oil solution.” Furthermore, the editorial noted:

¹¹ <https://monsanto.com/company/media/q/what-is-monsantos-opinion-on-agent-orange-and-ddt/>

¹² Kaley Deposition, Colella v. Monsanto, 11/17/2011, pages 41-43.

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Therefore, it is important that the suggestions of the Insecticide Division of the Department of Agriculture with regard to standardization and labelling be enforced; and that DDT sprays be not used on cabbage or similar vegetables after the heads have formed, or on crops to be fed to stock, until more is known of their limits of tolerance.

This caution was warranted because so little was known about DDT. Indeed, even the early studies investigating how DDT actually killed insects were not successful in revealing the mechanism of action. What was known, however, was that DDT must penetrate the insect skeleton and be absorbed into the fat-containing nervous system in order for DDT to kill insects; this penetration was due to the lipid solubility property of DDT.

Kirkwood and Phillips (1946)[101] studied the insecticidal properties of DDT and noted that the earlier insecticidal mechanism proposed by Lauger (1944)[101] was due to the “lipoid” property, stating:

Lauger’s suggestion is an extension of the Meyer-Overton theory of the mechanism of transportation and “storage” of the general anesthetics. He presented evidence to show that DDT acts on the insect’s nervous system...This evidence points rather definitely to a relationship between lipoid affinity and insecticidal activity and as such offers an explanation for the mechanism of action of 1, i-bis(pchlorophenyl) 2,2, 2-trichloroethane and related insecticides as suggested by Lauger.

In other words, DDT’s effectiveness as an insecticide was due to its lipid solubility -- not to a newly developed chemical/biological mechanism.

Two of the earliest studies to evaluate the lipid-solubility property of DDT that governed its bioabsorption and toxicity were published in 1944 (when Monsanto started production) by Smith and Stohlman[102] and by Nelson et al.[103] These studies were published the year Monsanto commenced DDT production.

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Smith and Stohlman noted that DDT was absorbed through the skin and that it had a “cumulative action,” indicating that its lipid solubility would cause it to accumulate until toxic concentration levels were reached:[102]

The toxicity of this compound, its cumulative action, and its absorbability through the skin under a variety of conditions of external application have made it desirable to devise a method for its identification in the tissues and body fluids.

DDT was not absorbed from the gastrointestinal tract in a water suspension but was absorbed when in a DDT-oil solution:

Gastro-intestinal absorption when given in aqueous suspension is irregular and poor, consequently the toxicity of the substance when given in this manner is much lower than when given in olive oil.

DDT’s toxicity was only seen with cumulative exposure as it built up in the body to toxic concentrations, which took 18–80 days:

The effects of DDT in experimental animals are cumulative, and small single doses given repeatedly lead to chronic poisoning. In a group of 10 rats of about 80 gm. weight, DDT fed at a level of 0.1 percent in a semisynthetic adequate diet containing 18 percent protein as casein was uniformly fatal in from 18 to 80 days...In rabbits the daily oral administration of 50 mg. per kg. in olive oil, a dose which by itself produces only slight or no demonstrable effects, resulted in cumulative effects terminating in death in from 15 to 23 days after a total dose of from 0.75 to 1.25 gm. per kg. had been given.

Smith and Stohlman concluded that DDT should be regarded as a health hazard because of its lipid solubility and cumulative toxicity:

The toxicity of DDT combined with its cumulative action and absorbability from the skin places a definite health hazard upon its use.

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Nelson et al. also stated that the lipid solubility of the oil-DDT solution controls toxicity and that powdered DDT applied to skin does not cause systemic toxic effects:[103]

Lesions caused by DDT in this group were relatively slight, probably because of poor absorption of dry DDT as compared with that dissolved in corn oil.

In the next year, study designs shifted from using laboratory animals to more environmentally relevant exposures in livestock. Based on the lipid solubility, investigators were interested in quantifying the magnitude of bioaccumulation and biomagnification as DDT was transferred through food chains.

In 1945, Dr. Woodard and his colleagues at the Division of Pharmacology at the U.S. Food and Drug Administration (FDA) published the seminal work on DDT bioaccumulation in breast milk.[89] They theorized that the lipid solubility of DDT enables it to be absorbed into the female body, where it bioaccumulates in the fat-rich breast tissue during pregnancy and that stored DDT is secreted into breastmilk. The DDT in breastmilk would then be absorbed by the suckling offspring to bioaccumulate in the bodies of offspring. This study showed not only that DDT could be transported through livestock and food chains to ultimately target human newborns, but that absorption by livestock could be very significant.¹³

Woodard et al. showed that when dogs were administered DDT for periods of time ranging from 138 days to 2 years, the pups readily bioaccumulated DDT in significant amounts; the DDT was stored in the dogs' fat tissues. Furthermore, DDT was eliminated only slowly from those stores after exposure was discontinued.

Perhaps more alarming—because of the obvious potential for exposures to human newborn children—was the degree to which DDT was secreted into the breastmilk of a lactating female dog. This finding obviously had real-life implications for environmental biological systems, as well as for humans. DDT was soon found to contaminate not only the environment but the U.S.

¹³ This study was published around the same time that Monsanto started DDT production. Furthermore, it was published in *Science*, one of the most prestigious and widely read scientific journals. *Science* is the official journal of the American Association for the Advancement of Science [AAAS].

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food supply, where women of childbearing age could bioaccumulate DDT and expose their offspring. This first study in dogs seemed to cause considerable concern for public health professionals; as in dogs, human breast milk has a high fat content and could likewise bioaccumulate DDT.

What prompted this study is noteworthy and pertinent to this case. Woodard cited one property as governing bioaccumulation of organic compounds: lipid solubility. He predicted that, based on the single property of lipid solubility, DDT would be bioaccumulative because “The high lipoid-water distribution ratio of DDT suggested that it might be preferentially stored in the adipose [fat] tissues of mammals fed DDT.” In other words, he made the logical prediction that DDT bioaccumulates based on its lipid solubility and that DDT is stored in fat.¹⁴

ACCUMULATION OF DDT IN THE BODY FAT AND ITS APPEARANCE IN THE MILK OF DOGS

The high lipoid-water distribution ratio of DDT suggested that it might be preferentially stored in the adipose tissues of mammals fed DDT. The toxicological behavior of this compound pointed also to the possible deposition in body fat.

Because the dogs were fed DDT, it meant that it was well absorbed from the gastrointestinal tract, distributed in blood, and stored in fat tissue. Exhibit 37 shows that extremely high levels of DDT were detected in fat, with the DDT fat concentration in one dog reaching 4,940 ppm when dosed at 80 mg/kg-day. This means the DDT not only bioaccumulated but also biomagnified. Even after the DDT exposure was terminated for approximately 3 months (80 days), 1 of the 2 dogs still had fat levels of 13 ppm. Both dogs secreted DDT metabolites after dosing was discontinued.

¹⁴ Given PCBs’ known lipid solubility, the same prediction could have made that very same year regarding PCBs.

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Exhibit 37. Excerpt from Woodard et al.: Bioaccumulation of DDT by Dogs

Dog no.	Sex	Weight kg	Daily dose mg/kg	Form of adminis- tration	Days duration	DDT in fat mg/gm
M-166	f	8.9	10	soln.	747	0.080*
81-196	m	10.0	10	soln.	747	0.024
1-20	f	6.5	50	soln.	443	1.65
81-195	m	10.4	50	soln.	747	4.94
1-35	f	6.9	80	solid	443	0.39
M-171	m	10.3	80	solid	443	0.67
After discontinuing dose for 81 days						
1-59	f	7.3	80	soln.	138	0.013
1-61	m	9.3	80	soln.	138	0.00

* For purposes of comparison, the intravenous lethal dose of DDT is of the order of 0.04 milligrams per gram body weight.

Source: Woodard et al. 1945.[89]

A further analysis of different fat stores revealed that DDT was distributed uniformly throughout the body, as it was detected in both subcutaneous (skin) and intraperitoneal (abdominal) fat.

Woodard confirmed his assumption that the lipophilic property of DDT is the sole determinant governing bioaccumulation and toxicity because no animals died when dogs were fed dry solid DDT (0/4 dogs), whereas the oil-DDT formulation resulted in the deaths of 14 out of 16 dogs.

In their investigation of the toxicokinetics of DDT, Woodard et al. found that a lactating dog dosed with 80 mg/kg-day-DDT secreted DDT into breast milk at concentrations of 40–60 ppm. In another lactating dog, a single dose of 50 mg/kg-day produced a milk concentration of 50 ppm in just 24 hours, demonstrating that not only was DDT readily absorbed, distributed, and secreted into the milk of lactating animals, but that the transfer was very rapid. Obviously, this shows that the DDT that had rapidly accumulated in the bitch was transferred to her litter of pups and that the same could be expected in humans.

A similar study published in 1945 by Telford and Guthrie also showed that DDT was quickly absorbed and “transmitted through the milk of white rats and goats” to their suckling

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young.[104]. This study was important because it was an “environmental” study on livestock that represented the fate and transfer of DDT in the food chain.

In the Telford and Guthrie study, DDT-induced tremors were used as the proxy metric for absorption (instead of direct DDT fat and milk analysis); exhibitions of excitation of the central or peripheral nervous system by the animals would indicate high absorption. Female rats with a 1-day-old litter were fed DDT and developed tremors between 6 and 13 days; their nursing young developed tremors between 14 and 15 days. Telford and Guthrie concluded that DDT was rapidly absorbed in the dams and transferred into the milk, stating, “Evidence was thus obtained that the toxic principle was transmitted through the mothers’ milk, since the young showed toxic symptoms before weaning.”

In addition, Telford and Guthrie revealed that DDT bioaccumulates and continues to bioaccumulate with chronic dosing, and that it can be transferred between species. When the researchers fed DDT to goats and then fed the goat milk to rats, the rats developed tremors and died within 2–9 days; milk from goats fed DDT for longer periods was more toxic. Telford and Guthrie stated:

Milk obtained from goats having received these dosages from 21 to 26 days was much more toxic than milk obtained from animals subjected to shorter periods of treatment. This indicated that DDT continued to bioaccumulate with continued exposures and once in fat tissue it remained for significant periods of time and was not rapidly eliminated.

Telford and Guthrie also showed that the DDT can be continuously transported through the food chain, and their findings showed biomagnification. For example, milk from a goat dosed with DDT for only 25 days was given to a “half-grown kitten,” the kitten died within 3 days, indicating that the DDT level in the breast milk was very high. When goats were administered feed contaminated with DDT and the collected goat milk was fed that to parturient rats (about to give birth), the suckling rat pups exhibited DDT toxicity.

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Like Woodard et al. (1945),[89] Telford and Guthrie also concluded that the lipid-solubility of DDT controls bioabsorption and produces the toxic effects they observed, stating:[104]

There is evidence that the toxic principle is concentrated in the fat globules of the milk, for butter, prepared from the milk of goats under similar treatment, when fed to rats produced typical tremors in the latter within 24 hours.

Telford and Guthrie noted that their findings had real-life implications for the transfer of DDT through the environment and, ultimately, for exposure to humans:

The data strongly suggest the need for more intensive research on the toxicity of milk from dairy cows ingesting DDT residues either from sprayed or dusted forage plants or from licking themselves after being sprayed or dusted with this insecticide.

These studies compelled other scientists to focus on environmental exposures and to determine whether the U.S. food supply was now at risk. As indiscriminant use of DDT was expanding, with large regional areas contaminated by widespread airborne spraying of DDT, pollution was now being taken seriously. The focus of scientific investigations turned to measuring the concentrations of food residues and making a determination regarding whether DDT residues in different commodities in the U.S. food supply could pose risks to the general population.

In a second June 1946 editorial in the *American Journal of Public Health*, the APHA took a position on protecting human health from exposure to, and toxicity from, DDT.[90] This was essentially a cautionary statement noting that, while DDT was a “wonder insect killer,” exposures to humans was a real concern and must be taken into account. APHA believed it was its professional responsibility to issue a caution that DDT is highly lipophilic and will bioaccumulate and biomagnify if used to spray crops or directly applied to human skin in an oil-DDT formulation because no regulations existed in 1946 regarding the judicious and safe use of DDT. The other emerging concern was that DDT was persistent.

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The editorial was written by Dr. Bishopp. The APHA specifically reached out to Dr. Bishopp (who was at the U.S. Department of Agriculture; the agency that had primacy over how DDT could be used) to prepare a Special Review Article. To summarize, Bishopp issued a forewarning that DDT posed real threats to public health because it was being released in massive levels to the environment. This could have catastrophic consequences. He noted that while DDT is a very powerful weapon against disease-carrying insects, scientists needed to begin looking more carefully at the potential human health impacts.

Bishopp also issued a prescient forewarning in 1947 about the longevity of environmental contamination from widespread use of DDT. This warning would prove to be correct. Although Bishopp could not know at the time, the one physical characteristic of DDT he noted was its “persistence,” which would later cause DDT to be identified as a global pollution problem (as would PCBs). Bishopp noted that, while persistence was an excellent property for DDT as an insecticide, great care should be exercised to prevent contamination of the U.S. food supply—with specific reference to protecting livestock. He stated:

One of the outstanding characteristics of DDT is its persistence. In fact, this is perhaps the major element in making it superior to many other insecticides. This persistence, however, makes it necessary to use care when applying it on crops or products intended for food or feed...The Bureau of Entomology and Quarantine does not recommend DDT for use on cabbage or similar vegetables after the heads or other edible parts are formed. Likewise, that bureau does not recommend its use on alfalfa, corn, or other crops to be fed to stock, especially dairy animals, until more is learned of the fate of small amounts ingested, especially with fatty materials.

By 1947, even major chemical companies were actively participating in, and funding research on, the topics of bioaccumulation, biomagnification, and human health risks from DDT. For example, American Cyanamid Company provided funding for a study by Howell et. al (1947) to investigate DDT bioaccumulation into cows and subsequent milk contamination. [105] This study was launched under actual environmental exposure conditions to determine whether the DDT sprayed on cows (to kill flies) was absorbed by the cows and secreted into milk that could

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potentially reach U.S. consumers. Spraying cows and dairy barns with DDT was becoming a concerning practice by 1947 as a method to control flies in dairy barns, as Howell noted:

considerable interest was created in the possibility that cows sprayed with this insecticide for fly control might produce milk containing toxic amounts of DDT.

Alarmed by earlier findings that lipid-soluble DDT was readily absorbed through the skin of other livestock and laboratory animals, Howell et al. initiated a series of investigations to determine whether DDT sprayed on the hides of cows absorbs and bioaccumulates. The researchers stated their concern:

When it was shown that DDT may be absorbed through the skin of animals and that animals fed massive doses of this material produced milk containing toxic doses of DDT, considerable interest was created in the possibility that cows sprayed with this insecticide for fly control might produce milk containing toxic amounts of DDT. To test this hypothesis a cooperative experiment was planned to show the effects of very heavy spraying and also the effects of the spraying schedule suggested for hornfly control in this area.

The results reported by Howell et al. show detections of DDT in milk from all cows after the 3-week exposure period during which cows were either sprayed daily or every 14 days with varying DDT concentrations ranging from 0.25–5.0% DDT, which corresponded to the actual exposure conditions that farmers were using. These exposures resulted in all cows secreting DDT in milk, with a maximum concentration of 33.6 ppm in milk from a cow sprayed for 20 days. [105]

Their findings also showed that once cows were sprayed and bioaccumulated DDT into their fattissue, the DDT remained and was not quickly eliminated. DDT was still detected in the milk for at least another 3.5 months (120 days). Daily measurements showed that DDT-contaminated milk was still detected on December 1, although DDT exposure had been terminated on September 30. [105]

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In addition to the concerns regarding bioaccumulation of lipophilic DDT in milk (which was confirmed in 1946), scientists were concerned about the U.S. meat supply and predicted that beef muscle fat could also be contaminated. A study by Carter et al. (1948)[106] showed that DDT remained resistant to degradation, no matter the method of cooking, once DDT was absorbed into muscle fat tissue: “The results of the chemical analyses, given in Table 1, indicate that the DDT in the beef was not materially decomposed or lost during the cooking.” When beef cattle were fed DDT-contaminated hay, the highly lipophilic compound accumulated in muscle fat and was not appreciably degraded, even after four different cooking methods.[106]

In 1947, Rubin et al. investigated the bioaccumulation of DDT in eggs laid by chickens administered feed with different DDT residue concentrations.[107] The DDT bioaccumulation appeared to follow a dose-bioaccumulation relationship.

Rubin et al. concluded:

It is apparent that deposition of DDT in the eggs increased as the dietary intake of this compound increased but reached a maximum when the intake was 0.125% of the diet.

One year later, in 1948, biomagnification through the food web became a major concern for public health officials and regulatory agencies, who now saw that low levels of DDT in the U.S. food supply were producing very high levels in fat stores. This prompted Dr. Fitzhugh, of the Food and Drug Administration, to conduct a biomagnification study:[20]

Because small amounts of DDT in animal food cause the storage of large amounts in animal products which are used in enormous quantities by man, the question of the safety of DDT on and in food products becomes critically important...The general availability and effectiveness of DDT as an insecticide introduce the possibility of its widespread occurrence in food products. The most serious source of danger from the use of DDT is the repeated ingestion of small amounts that cling to forage, fruits, and vegetables that have been treated with this insecticide.

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The Fitzhugh (1948) study was intended to evaluate the possibility that widespread use and availability of DDT resulting in low levels of DDT detected in fat-containing foods during FDA's food surveillance could inexorably build up as DDT was transferred from one animal to another up the food chain. The greatest impact of biomagnification would be in humans.

In effect, he was raising the same issue as Bishopp (1946).[90] While Bishopp was only able to predict biomagnification through the complex food web, Fitzhugh and his staff at the FDA were in a position to *test* this possibility. As discussed previously, many at the time were of the opinion that DDT was still safe to use because it was virtually nontoxic, based on a single acute dose. Now knowing that cumulative exposures to livestock led to bioaccumulation and secretion into milk because DDT was so highly lipophilic, each subsequent exposure led to more DDT accumulating in the fat tissue increasing the body burden. In short, DDT levels were compounded and magnified with continuous daily exposures where the concentration in body fat far exceeded the concentration in their feed .[20]

The storage of DDT in the tissues, especially in the fatty tissues of animals ingesting small amounts, has been demonstrated in cows, monkeys, dogs, rats, rabbits, and poultry. DDT has been shown to be secreted in the milk of cows, goats, dogs, and rats. Other animals fed the milk from the DDT-treated animals showed toxic symptoms. All the DDT in the milk appears to be concentrated in the butterfat portion and to be transferred to the butter; therefore, a relatively small amount of DDT in the whole milk results in a significant amount in the butter. The quantities of DDT that are stored apparently depend both on the level of ingestion and on the length of time over which the intake occurs.

Fitzhugh's major concern regarding the food supply was that each incremental chronic ingestion of contaminated food (even if the dose was low) could ultimately result in the high levels of DDT in fat stores. In other words, he was stating the obvious: chronic doses are additive, amplifying the toxic effect, with the sum of each dose eventually equaling a very large single dose.

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It should also be noted that human infants were then being identified as the most sensitive subpopulation:

In long term experiments dosage levels of DDT from 10 to 200 p.p.m. in the diet produce relatively similar amounts of DDT in the fat (Table I). An animal may store amounts equivalent to several acute intravenous lethal doses without showing any obvious signs of intoxication. The accumulation of appreciable quantities of DDT in animal tissues at low dietary levels (all levels appear to produce storage in fat) poses a difficult problem, since many animal products are, used for human consumption. This may be especially important in the case of infants, whose chief food is milk. The presence of small amounts of DDT in animal food, therefore, assumes the same importance as relatively larger amounts on fruits and vegetables consumed directly by man.

Fitzhugh's empirical evidence of this biomagnification phenomena demonstrated that a low daily dose was biomagnified in the tissue of rats. Some of the rats had a biomagnification factor of up to 27-fold. That is, the concentration in body fat (perirenal; kidney fat) was 27 times the dose concentration the rat was fed (although there was much variation among the rats).[20]

Fitzhugh noted that, when small daily doses yielded the biomagnified DDT fat levels, insidious and unexpected toxic effects expected from a single large dose were produced. He reasoned that DDT is sequestered in fat tissue when administered at lower levels, where it is safely stored and cannot produce DDT-induced neurotoxicity. This is because toxic chemicals are unable to produce toxic effects when they are bound to proteins or fats. It is only when they become "unbound" and circulate in a "free" state that they become mobile in the blood circulation and can reach the brain or peripheral nerve to attack the nervous system. There is a dynamic equilibrium between DDT stored in lipoproteins in the blood and in fat tissue. Fitzhugh knew that when the ratio between bound and free DDT shifts with fat loss (as occurs with illness, disease, or dieting), more free DDT becomes available to reach the target organ (nervous system). Fitzhugh tested this phenomenon by removing the rat food (essentially mobilizing more free DDT because fat was now being consumed as an energy source) and confirmed that DDT-

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induced tremors were produced. This showed the additional risks DDT poses to the U.S. general population as individuals intentionally or unintentionally (disease and illness) mobilize or lose body fat, since DDT is then free to attack the liver or central nervous system. It would also increase the cancer risk:¹⁵ [20]

The withdrawal of food from animals on high dosage levels of DDT produces characteristic DDT tremors. This effect occurs both in starvation experiments with DDT-treated animals and in DDT-treated animals made sick by an infection {2}. In the latter case the animals supposedly were metabolizing their body fat containing the DDT in the same manner as a starved animal. This effect could be important in cases of human illness where there is an appreciable storage of DDT in the body.

The 1948 Fitzhugh study presented clear, simple, and unequivocal empirical evidence that DDT bioaccumulate and biomagnifies, and that this property is directly and unmistakably due to DDT's high lipid solubility. Furthermore, Fitzhugh did not require any elaborate laboratory equipment or sophisticated study designs to prove these facts. He predicted DDT would bioaccumulate and biomagnify and used simply designed experimental methods to prove his prediction. Fitzhugh employed the same experimental animals, study designs, and methods that were used in the late 1930s.¹⁶

A more sophisticated study of absorption, distribution, and elimination of DDT and dichlorodiphenyldichloroethane (DDD), which have the same lipophilic properties, was published in 1949 by Finnegan et al.[108] Like the Howell et al. (1947) study,[105] this too was funded by a chemical company—Rohm and Hass Company. By 1949, DDT had been in widespread use, with massive quantities released into the environment. Finnegan's study investigated the toxicokinetics and combined absorption, storage, and excretion of DDT. After dosing dogs with DDT and DDD (a major degradation product of DDT) for 2 and 4 weeks,

¹⁵ Fitzhugh and Nelson had shown just a year earlier that DDT causes cancer[123]

¹⁶ Monsanto could have performed a study identical to Fitzhugh's investigation in the late 1930s on PCBs.

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Finnegan et al. measured the content of these two pesticides in all major organs. Their results are tabulated in Exhibit 38. Not surprisingly, fat tissue and organs rich in fat had the highest concentrations of both compounds.

Exhibit 38. Excerpt from Finnegan et al.: DDD and DDT Content in Dog Tissues After Oral Administration

TABLE I. DDD and DDT Content of Tissues of Dogs to Which the Insecticides Had Been Administered Orally Daily for Periods of 2 and 4 Weeks.										
Insecticide	Insecticide content, mg per kg of tissue									
	DDD					DDT				
	2 wks		4 wks			2 wks		4 wks		
	D-4	D-5	D-1	D-2	D-3	T-4	T-5	T-1	T-2	T-3
Dog No.										
Liver	0	0	1.6	0	24	0	0	0	0	0
Kidney	15	4.3	13	14	15	4.9	0	14	7.2	9.6
Heart	3.8	0	11	12	13	0	3.4	4.9	8.1	3.4
Brain	0	0	3.5	4.1	5.2	1.3	0	2.5	3.9	1.2
Lung	0	0	1.9	3.9	lost	0	0	0	0	0.8
Pancreas	0	0	8.9	29	12	0	3.4	14	9.4	8.8
Spleen	0	1.7	0	12	4.7	0	0	2.2	3.6	0
Adrenal	0	0	150	0	210	0	0	83	63	62
Fat	76	270	880	360	300	29	100	910	400	200
Muscle (gastroc.)	7.6	5.2	lost	20	28	8.4	5.5	12	14	18
Skin	90	7.2	28	128	18	82	73	0	6.4	3.3
Mammary gland	—	—	—	—	—	—	—	2.2	—	21
Fecal excretion mg/kg body wt, 48 hr	0.9	4.2	3.9	2.2	3.9	lost	0.03	0.01	0.5	0.8

Source: Finnegan JK, Haag HB, Larson PS. 1949.[108]

In a set of additional experiments, Finnegan et al. investigated whether DDT could pass the placenta circulation from the maternal blood supply to the developing fetus. In these experiments, some of females became pregnant during the dosing exposure and bore litters of pups, some of which were stillborn. The surviving pups were killed before they were able to suckle breast milk. The researchers repeated the earlier experiments and measured the body burden levels in both the newborn (but not sucking pups) and stillborn pups. With this experimental protocol preventing the pups from suckling breast milk, they could directly determine if DDT crossed the placental barrier to expose the developing fetal pup. Again, this experiment was based on the prediction that lipid-soluble DDT would readily pass the placental barrier, as other important lipids and lipoproteins do. What Finnegan et al. found was an unexpectedly high bioaccumulation of DDT in the pups (although they noted that they lost part

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of the sample for the T-1 pups, which accounts for the relatively low DDT levels detected in those dogs). They stated:

Analysis of the pooled carcasses of the 5 stillborn pups from one of the 4-week DDD dogs (D-1) showed a content of 3.7 mg per kg DDD. Similar analyses of individual carcasses of (the 2 newborn pups from dog T-1 and the 2 newborn pups from dog T-3 (both 4-week DDT dogs) gave average values of 1.3 mg per kg for the first pair and 0.04 mg per the for the second. It was thought that the latter result was low owing to possible loss of part of the sample. These results demonstrate transfer of both DDD and DDT across the placenta.

Their findings added to concerns regarding DDT for two reasons. First, they showed that human lifetime exposures do not start after birth with breastfeeding, but that exposures and bioaccumulation start in the womb. Second, their results raised the possibility of birth defects and developmental abnormalities since DDT exposures to the fetus start very early in development—before organogenesis—when maternal–fetal blood connection is first established. The scientific work to this point had shown biomagnification during breastfeeding of the newborn, but fetal abnormalities were a now a concern because the fetus had been shown to be exposed to the lipid-soluble DDT. In fact, Fitzhugh concluded that transplacental transfer of DDT was greater than newborn suckling of breastmilk:

This again is indicative of a high degree of placental transfer of DDT and further suggests that the fetus is more liable to the accumulation of DDT than is the suckling offspring, despite the fact that DDT has been shown to be secreted in the milk¹⁷.

Once again, Finnegan et al. identified DDT's lipid solubility as the governing property of DDT. Moreover, they noted the same scientific processes that I previously discussed with regard to the

¹⁷ Given that DDT and PCBs share the same lipid solubility property, Fitzhugh's conclusion could have been extended to PCBs. Based on Fitzhugh's study, PCBs should have been understood to be absorbed from maternal blood into fetal blood, resulting in exposure of the developing fetus in the womb, with unknown health effects.

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Meyer-Overton rule explaining bioaccumulation of both DDT and DDD. That is, both compounds are chemically similar, and both are similarly soluble in olive oil.

It seems that, in general DDD and DDT were deposited in fat to a similar degree. This is in agreement with the thesis of von Oettingen and Sharpless that since the 2 compounds have similar solubility's in olive oil they would probably be stored to about the same degree in fat.

It should be noted that, although this was the first empirical evidence of a specific lipophilic compound transferred from maternal blood to fetal blood (namely DDT and DDD), it was well-established a decade earlier—in 1937—that lipids and lipophilic substances readily pass through the placental circulation and are absorbed into the developing fetus.[109], [110] Finnegan et al. noted that this new finding was more significant than those of earlier studies revealing that DDT was secreted into breast milk. Direct blood transfer of lipid-soluble DDT from mother to fetus increased body burden more than subsequent newborn suckling of breastmilk:[108]

This again seems indicative of a high degree of placental transfer of DDT and further suggests that the fetus is more liable to the accumulation of DDT than is the suckling offspring, despite the fact that DDT has been shown to be secreted in the milk.

To summarize, the chemical industry knew by 1949 that lipophilic chemical compounds like DDT readily cross the placental circulation to the fetus and are also secreted into the mother's milk. This means that the body burden of such lipophilic compounds would already be significant at birth and that the body burden would only increase with subsequent breast-feeding.

Additionally, when bioaccumulation of DDT fetal and newborn body burden is considered based on body weight, newborns would have the largest body burden at this stage of life. By 1950, scientists had established that DDT bioaccumulated and biomagnified in the food web and that the developing fetus and newborn were of growing concern. Newborn animals not only accumulated high levels of DDT, but they were at particular risk because they were undergoing

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organogenesis. While many previous studies dosed animals at elevated DDT levels (thought to be above what the general population would receive in its daily diet) in experiments, it was unknown whether DDT would bioaccumulate at lower doses—those levels closer to the “assumed” daily dietary intakes. However, no governmental agency had started a food surveillance-sampling program at this time, so the residue levels were unknown. To determine if lower doses would also be bioaccumulative and biomagnify, Laug et al. (1950) conducted experiments at very low doses (far lower than would be reported in food residue studies).[21] The lowest DDT level they used was 1 ppm. They explained their rationale:

Storage within the organism of any toxic substance foreign to its tissues may be regarded as a potential hazard. As reported from this laboratory the DDT content of the adipose tissues of animals consuming high concentrations of DDT in their diets can be 100 times as great as in other tissues. While these data clearly indicate DDT storage in fat when DDT is ingested in large amounts, it does not necessarily follow that storage would occur when very small amounts of DDT are ingested. In view of the widespread use of DDT as an insecticide, the content of a variety of foods may be expected to be of the order of 1 .0 p.p.m. more or less.

Exhibit 39 presents Laug et al. findings that food residues as low as 1 ppm did indeed bioaccumulate and biomagnify in perirenal fat.

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Exhibit 39. Excerpt from Laug et al.: DDT Content in Perirenal Fat, by Dietary Level of DDT

TABLE 1										
<i>The storage of DDT in the perirenal fat of rats at various dietary levels of DDT</i>										
P.P.M. DDT IN DIET	P.P.M. DDT IN PERIRENAL FAT								STORAGE RATIO†	
	After 15 weeks		After 19 weeks		After 23 weeks		After 27 weeks			
	M	F	M	F	M	F	M	F	M	F
Control*			7.8	6.2		7.1	8.1	9.4		
0.12			3.4	4.5						
1	15	20	24	38	21	25	17	33	21	29
	11	16	27	30	33	33		37		
5	61	88	68	108	64	111	47	106	12	20
	45	107	62	106	60	110	54	74		
10	65	137	79	155	84	165	78	132	8	15
50	350	642							6	12
	217	533								

* Additional control animals housed in different rooms: the fat of two year-old males contained 13 and 13 p.p.m., respectively; the fat of two 8-month-old males contained 10 and 5.8 p.p.m., respectively.

† Concentration of DDT in Fat
Concentration of DDT in Diet

The concentration of DDT in the fat represents the average of the 15, 19, 23 and 27-week groups.

Source: Laug et al. 1949.[21]

As shown, a concentration as low as 1 ppm DDT in the diet was not only bioaccumulated, but the storage ratio (DDT fat concentration/DDT in diet) was much higher at lower doses. This means that the ability of DDT to bioaccumulate was higher at lower doses. Their results also showed a gender sensitivity in that female rats accumulated DDT to much greater fat concentrations, which, in turn, meant they would transfer larger amounts of DDT to their offspring. Females fed a diet with DDT residues at 1 ppm resulted in fat concentrations of 20, 38, 25, and 33 ppm at 15, 19, 23, and 27 weeks, respectively. Another interesting finding from the Laug et al. study is that DDT bioaccumulation occurred even in the control animals (shown in 0 as Control*). This is significant because it revealed that the environment was ubiquitously contaminated with DDT. Despite the fact that control animals were not dosed with DDT and were housed in a separate animal room, DDT was detected in their body fat. Laug et al. concluded this result showed extremely low levels of DDT residues in their purchased commercial rat chow and even at these “extremely” low dietary levels, animals were bioaccumulating DDT. Laug et al. also stressed that this demonstrated the “avidity” of DDT in that even miniscule amounts could lead to bioaccumulation:

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The finding of DDT in the fat of the control animals demonstrates the avidity with which the adipose tissue can accumulate DDT from extremely small dietary residues. It should be emphasized that the finding of DDT in the fat was not restricted to the animals serving as controls for this series, but was observed also in other animals housed in different laboratories for longer periods of time (see footnote, table 1).

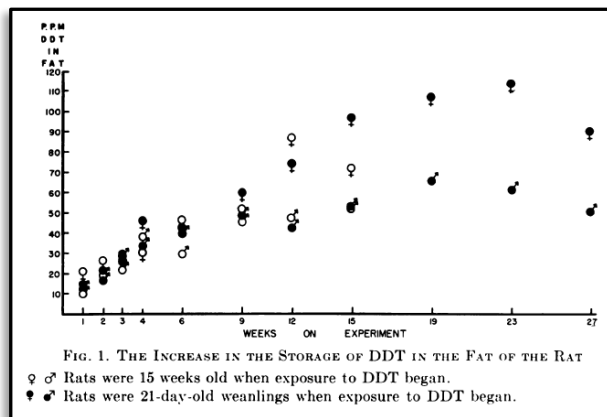
He further stated that there was no “floor” (minimum dose level) below which DDT would not bioaccumulate.

DISCUSSION. The experiments reported here show that very small quantities of DDT in the diet are reflected in storage in the fat of rats. Furthermore, it appears that as the amount of DDT offered the rat in its diet decreases, the percentage thereof which goes into storage increases. It may be concluded therefore that there is no “floor” of dietary concentration below which the storage of DDT does not occur.

Laug et al. prepared a graph demonstrating how DDT bioaccumulation inexorably increases with chronic exposure over a 27-week exposure period (Exhibit 40). This graph mirrors the types of exposures that would be expected in the U.S. general population.

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Exhibit 40. Laug et al. Excerpt: Increase of DDT Storage in Rat over Time



Source: Laug et al. 1949.[21]

After showing that DDT body burden levels would build to potentially toxic levels with chronic exposures, Laug et al. turned their attention to the elimination rate to determine how fast DDT would be secreted in stool or urine if DDT exposures were discontinued. DDT would be eliminated very slowly, with fat stores still at high levels (73%) after 1 month at a low dose (1 ppm); at a higher dose (50 ppm), DDT would still be elevated after 3 months (26% in female rats).

Two years before the Laug et al. study was published (1950), Carter (1948) published one of the first analytical surveys of DDT.[111] His results were troubling because he detected DDT at levels much higher than 1 ppm (the level used by Laug et al). Working in collaboration with food cooperatives and industry, he investigated how DDT was routinely used and followed the DDT literally from the “ground up” to measure bioaccumulation and other impacts on food chains in order to get a clear picture of the potential contamination of the U.S. food supply. Their goals were as follows: 1) determine the DDT residues on fruits, vegetables, and forage crops; 2) measure the absorption of DDT residues by plants and its translocation into the edible portions from applications to the aerial parts; 3) measure absorption and storage of DDT in the organs and tissues of farm animals that received small amounts ingested with the food; 4) quantify DDT content of milk from cows fed silage containing DDT residues; 5) evaluate the effect of cooking

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meat from animals that had stored appreciable amounts of DDT in their tissues as a result of having been fed rations containing this compound; and 6) measure the DDT content of eggs from hens receiving DDT in their feed. Carter's experiments not only quantified the residue amounts of DDT that would contaminate specific food items, but provided a wider perspective on the complex fate and transport environmental processes controlling how DDT moved and biomagnified through the various trophic levels. For example, Carter determined what amount of DDT deposited in soil would be translocated up into the edible plant parts that would be fed to livestock, where the DDT would bioaccumulate into fat tissue of fish, poultry, meat, milk, eggs, etc. His analysis showed that potential DDT contamination of food was likely well above levels of 1 ppm that were "assumed" by Laug et al. in 1950.[21] For example, cows were raised on pea vines and had a residue concentration of 50 ppm (Exhibit 41).[111]

Exhibit 41. Excerpt from Carter: DDT Residues on Various Crops

TABLE I. DDT RESIDUES ON CROPS			
Crop	DDT Treatment ^a	Time of Sampling	DDT Residue, P.P.M.
Apples	Sprays, 1 lb. per 100 gal.	Harvest	1-12.5
Peaches			
Unbrushed	Sprays, 1 lb. per 100 gal.	Harvest	6-23
Brushed	Sprays, 1 lb. per 100 gal.	Harvest	3-14
Pea vines	Aerosols, 0.3-0.5 lb. per acre	Maturity	15-50
	Dusts, 0.5-1 lb. per acre	Maturity	2-10
Shelled peas	Dusts, 0.5-1 lb. per acre	Maturity	None
Alfalfa	Dusts, 1-2 lb. per acre	Hay cutting	2-48
^a 4 cover sprays for apples, 2 for peaches.			

Source: Carter 1948.[111]

Carter attributed the total environmental "load" in all food to be due to the stability or persistence of DDT because, even when DDT was applied early in the growing season, it still contaminated the crops at harvest and would then be bioaccumulated into livestock administered the contaminated feed:

Insecticide formulations containing DDT applied to field crops during the growing season generally result in residues which persist until the crop is

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harvested. When forage crops containing large amounts of DDT residue are fed to farm animals, DDT may be stored in the tissues and eliminated in the milk.

After slaughter and analysis of different butchered cuts of meat, pigs fed corn meal and ground beef containing 5 ppm DDT revealed that the lipophilic property of DDT was the sole determinant factor in the disposition of DDT in fat:

The pigs were butchered and the carcasses separated into three portions—lean meat, leaf fat, and external plus intramuscular fat. The amounts of DDT from the two lots were 2 and 1.7 p.p.m. in the lean meat, 15.6 and 11.4 p.p.m. in the external and intramuscular fat, and 17.6 and 11.4 p.p.m. in the leaf fat.

DDT content in milk depended on the silage DDT residue concentration in food, which ranged from zero to 25 ppm. In eggs, the concentration was much higher. When chickens were fed a diet with DDT levels of 0.031, 0.062, 0.125, and 0.250% DDT, the concentrations found in the eggs were 0, 180, 240, 360, and 320 ppm, respectively, showing significant biomagnification even when limiting the food chain from chicken to egg. Based on the totality of his analyses, Carter attributed contamination of the food supply on DDT's environmental persistence and lipid solubility:

CONCLUSIONS Insecticide formulations containing DDT applied to field crops during the growing season generally result in residues which persist until the crop is harvested. When forage crops containing large amounts of DDT residue are fed to farm animals, DDT may be stored in the tissues and eliminated in the milk."

By 1947, the U.S. Department of Agriculture was concerned that indiscriminant use of DDT could lead to contamination of the U.S. milk supply after considering all the published studies summarized here. Shepherd et al. (1949) conducted a controlled environmental study on feeding milking cows both alfalfa and pea vine silage with various residue levels of DDT.[112] They stated the department's alarm:

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Insecticides containing DDT now are being used on various crops grown as feed for milking cows. The relationship between the amount of DDT residue on the crop when fed, or the amount of DDT ingested by the cows, and the amount of DDT that may appear in the milk is not too well known. It is possible that enough DDT may be secreted in the milk to make it detrimental to consumers, especially if consumption of such milk is continued over a long period of time, since Kunze et al. (3) have reported that as little as 5 p.p.m. of DDT in the diet of the rat for 4 to 6 months will produce histopathological alterations of the liver.

They identified the seminal previous studies that were begun in 1946 that prompted their work:

Carter et al. (1) fed pea vine silage to milking cows at the rate of 3 lb. per 100 lb. of body weight. The silage contained 2.7 to 5.4 μ g of DDT per g. on a fresh basis and 7.7 to 18.7 μ g on a dry weight basis. The daily intake of DDT per cow was approximately 44 to 88 μ g. The DDT content of the milk was less than 0.5 μ g per g. Wilson et al. (5) found 15 μ g of DDT per g. in the milk from cows fed pea vine silage that provided an intake of about 1.5 g. of DDT per day per 1,000 lb. of body weight. These same investigators also found 44 μ g per g. in the milk from a cow that received 24 g. of DDT per day. This report gives the results of recent studies showing the concentration of DDT in the milk from cows fed alfalfa hay that had been treated with DDT under field conditions.

Although their study was a field study, Shepherd et al. applied the amount of DDT that was routinely used to control the potato leafhopper:

In August, 1947, a field of alfalfa, from which the third cutting was to be taken, was treated with different amounts of DDT by means of an aerosol machine. Part of the field was treated with 0.6 lb. of DDT per acre, the rate usually recommended for control of the potato leafhopper, and harvested 20 days later.

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Data for one cow show that DDT accumulated in milk while the cow was fed contaminated pea vines and after the DDT was terminated (on April 14, 1948).

Their findings were a stark warning that the entire U.S. milk supply could be contaminated with DDT. Shepherd et al. also showed that once DDT bioaccumulated in milk cows, it continued to contaminate the milk for long periods of time after exposure ceased (Exhibit 42).

Exhibit 42. Excerpt from Shepherd et al.: Summary of Findings

SUMMARY
1. Alfalfa treated with 2.4 lb. of DDT per acre, in the form of an aerosol, and fed to cows at the rate of 1 lb. of hay per day per 100 lb. of body weight produced milk containing up to 10.1 γ of DDT per g. or 259.1 γ per g. of butterfat. The daily intake of DDT was as high as 903 mg. and the output in the milk was as high as 265 mg.
2. Alfalfa treated with 0.6 lb. of DDT per acre and fed to cows at the rate of 1.5 lb. of hay per 100 lb. of body weight produced milk containing up to 0.9 γ of DDT per g.
3. The output of DDT in the milk varied from 5 to 30 per cent of the intake. The DDT appeared in the milk after a very few days of feeding, and in one case was present in appreciable quantities after 3 days of feeding.
4. After the feeding of DDT hay was discontinued, DDT was detected in the milk for 160 to 170 days when large quantities of DDT had been fed and for only 30 to 40 days when small quantities had been fed.

Source: Shepherd et al. 1949.[112]

8.3. The link between DDT Food Residues and Body Burden continued to be developed after 1950.

All of the DDT studies described above were published 1944–1950 and demonstrated that DDT's high lipid solubility resulted in bioaccumulation and biomagnification in animals and humans. After studies through 1950 provided overwhelming empirical evidence of DDT bioaccumulating and biomagnifying, scientists and the regulatory community continued to further quantify food contamination, as well as body burden in the U.S. general population. I summarize these efforts in the remainder of this section.

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Once it had been established that DDT food residues were elevated, the next step was to confirm that was directly linked to increased body burden in the general U.S. population. Pearce et al. (1952), from the U.S. Public Health Service, began a surveillance study in 1949 to measure DDT and dichlorodiphenyldichloroethylene (DDE) in human fat.[113] They initially measured the levels in individuals who had known high exposures to DDT. In 1952, Pearce extended those initial investigations to measuring the DDT concentration in fat stores from persons who had no known exposure to DDT or who had not been exposed for “some time.” This group was assumed to represent the U.S. general population exposed to DDT residues only through consuming food. Pearce et al. based their sampling on two cohorts—neither of which had known direct DDT exposures—and found that both had bioaccumulated very significant levels of both DDT and DDE in their fat stores.

Based on this data, Pearce et al. stated that the levels of DDT “in the fat of individuals of the general population arises mainly through contamination of a number of common foodstuffs.” They also raised the possibility that DDT health risks may have been previously underestimated because those studies had not measured DDE levels, so the toxicity from this second group of DDT-like compounds would have been ignored. Pearce et al. showed that both DDT and DDE were found together in every sample.

If DDT is slowly degraded after deposition in the fat, it would seem of great importance in assessing any potential danger from food contamination with DDT. In any case, the evidence for the occurrence of substantial proportions of DDE suggest that the possible health hazards involved in the widespread use of DDT need to be reconsidered and further investigated.

In a subsequent experiment to verify the results of Pearce et al. that members of the general population had significant levels of DDT in their fat and that this was not a spurious finding, Mattson et al. (1953) (also at the Public Health Service) obtained and measured DDT in human archival autopsy fat specimens dating back to 1938 and 1940 (prior to the manufacture of DDT in approximately 1944).[114] They found no evidence of DDT or DDE, which they assumed were breakdown products. A summary of their DDT and DDE data is presented in Exhibit 43.

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Exhibit 43. Excerpt from Mattson et al.: DDT and DDE in Human Archival Fat Specimens

Table XI. Analyses of Human Fat Samples Taken in 1938 and 1940							
Year Taken	Net Grams of Fat	Wave Length, $M\mu$		Equivalent of ^b Absorbance in Terms of			
		520	597	p,p' -DDE, γ	p,p' -DDT, γ	p,p' -DDE, p.p.m.	p,p' -DDT, p.p.m.
1938	2.5	0.013	0.008	1.1	0.8	0.4	0.3
1940	1.9	0.004	0.008	0.1	0.9	0.1	0.5
1940	1.6	0.010	0.009	0.7	1.0	0.4	0.6

^a Corrected for reagent and Davidow column blanks.
^b No Schechter-Haller colors in evidence.

Source: Mattson et al. 1953.[114]

With this verification step completed, Mattson et al. stated, “The writers believe that DDT and DDE are contaminants of human fat of the general population.” Thus, the DDT residue levels quantified by Carter now appeared to be directly linked to the general U.S. population. In a fairly comprehensive analysis of DDT residues in the general food supply, Walker and his colleagues at the Public Health Service (1954) launched a detailed analysis of the U.S. food supply based on actual meals that were being consumed by average Americans (Exhibit 44).[115] They stated:

To determine the amounts of DDT and DDE ingested during normal food intake, 18 meals were obtained from restaurants and 7 were obtained from a correctional institution. Most of the food prepared by the restaurants was not locally grown. Much of the food consumed at the correctional institution was produced within the institution itself. Regional items, such as fresh sea food and unusual foods, were avoided, so that a representative cross section of food items consumed by the public could be obtained. Home-cooked meals also were avoided because of the difficulty of obtaining a representative cross section.

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Exhibit 44. Excerpt from Walker et al.: DDT and DDE Content of Typical U.S. Meals

Meal	Total Weight (Including Beverage), Grams	Total Found, γ		Ratio of DDE/DDT
		DDT ^a	DDE ^b	
Morning				
1	527	27.5	12.5	0.46
2	443	62.5	30.5	0.49
3	522 ^c	59.5	24.5	0.41
4	728 ^d	48.0	26.5	0.55
5	536 ^e	70.0	47.5	0.68
6	731	27.5	8.5	0.31
7-IM	805	8.5	5.0	0.59
8-IM	383 ^f	10.0	5.0	0.50
Mean	584	39.2	20.0	0.51
Noon				
9	701 ^g	40.0	23.5	0.59
10	848	163.5	44.5	0.27
11	687	16.5	21.0	1.27
12	987	17.0	17.5	1.03
13	805	65.5	50.0	0.76
14	689	37.5	58.0	1.55
15-IM	1508	34.5	15.0	0.44
16-IM	652 ^h	79.0	25.5	0.32
17-IM	548	71.5	30.0	0.42
Mean	825	58.3	31.7	0.54
Evening				
18	666 ⁱ	118.0	43.0	0.36
19	900	46.0	40.5	0.88
20	1017 ^j	161.5	34.5	0.21
21	1196	51.0	31.5	0.62
22	1108	32.5	27.0	0.83
23	914	34.0	12.5	0.37
24-IM	1083 ^k	50.0	30.5	0.61
25-IM	1288	39.5	27.0	0.68
Mean	1022	66.6	30.8	0.46
Mean of all meals	811	54.8	27.7	0.50

IM Institutional meals.
^a Calculated as technical DDT.
^b Calculated as recrystallized DDE.
Amounts lost on analysis and not included in totals. ^c 140 grams. ^d 49 grams. ^e 42 grams. ^f 192 grams. ^g 471 grams. ^h 75 grams. ⁱ 193 grams. ^j 268 grams. ^k 51 grams.

Source: Walker et al. 1954.[115]

Walker et al. found that the U.S. general population was chronically exposed to elevated levels of DDT, based on residues measured in normal meals in 1954—less than 10 years after the insecticide started being used as a pesticide throughout the nation. Although Walker et al. stated that the daily ingestion of 0.0026 DDT by an average man would not likely produce systemic toxicity, they acknowledged that there was no precise toxicity information available for humans. Furthermore, they were solely focussed on systemic toxicity or “injury”:

To date there is no precise information as to the amount of DDT which can be consumed by humans over a long period of time without the possibility of adverse

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results. Basing his conclusion mainly on chronic toxicity studies conducted on laboratory animals, but taking a safety factor into account, Neal (77) estimated that 5 mg. of DDT can be ingested daily without untoward effects... Fitzhugh (7) and Heyroth estimated that man can ingest 2.5 mg. of DDT daily over a long period of time without injury.

However, they did not consider that even these low DDT exposures could cause DDT-induced cancer. Their summary completely ignored the study by Fitzhugh et al. (1947) that demonstrated DDT was carcinogenic. Fitzhugh et al. stated:

Taken together, the 15 rats having either liver tumor or nodular adenomatoid hyperplasia are numerically enough to strongly suggest a distinct although minimal tumorigenic tendency of DDT...The observations of this experiment show that chronic poisoning with small amounts of DDT is characterized by degenerative changes in the liver and other organs. This toxicity places a definite and inherent danger in the consumption of small amounts of DDT for a long time.

In 1951, Laug et al. reported the presence of DDT in human breast milk.[116] They reported that, out of 32 women, “DDT was present in all except three of the specimens of human milk examined,” with an average concentration of 0.13 ppm. In response to the amassed human studies, the American Medical Association (AMA) started speaking out regarding the dangers of bioaccumulating and biomagnifying DDT in human fat and the results of those high levels being detected in the U.S. population. In a 1951 editorial in the *Journal of the American Medical Association*, the AMA issued a warning about the potential consequences of the biomagnification of DDT.[117] Perhaps even more importantly, the editorial educated scientists and other health professionals for the first time about the critical function fat provides to health. In so doing, the AMA corrected many misconceptions—namely, that fat is just a depot or repository that holds fat like a “sponge.” Most scientists at this time regarded fat tissue (known as *adipose tissue*) as a static nonmetabolic tissue that simply absorbed toxic lipophilic chemical compounds like DDT and PCBs. The AMA corrected this misconception by stating that adipose

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tissue plays a vital role in many metabolic functions, and the accumulation of toxic lipophilic compounds could compromise health:

Adipose tissue is not merely connective tissue which functions in a passive manner as a fat depot; it is also a structure possessing functions that have been compared to those of a ductless gland... The tissue has a rich blood supply, and the mobilization and deposition of the fat is regulated by endocrine as well as nervous (sympathetic) influences... Nevertheless, enzymatic activity is carried out by the fat cells, which can accumulate glycogen, change carbohydrates into fat and transform one fatty acid into another. It has been asserted that, as part of the reticuloendothelial system, blood-forming functions may become established in adipose tissue under appropriate conditions, and that the cells of the omentum are capable of forming antibodies.

As I noted in a previous section, the DDT stores are mobilized as part of the normal fat mobilization cycle of all adipose tissue, and the normal use of fat as an energy source releases “free” DDT that can then target different organs. DDT is also released in significant amounts in illness and disease—at precisely the time when further toxic insults can compound a person’s illness. The AMA noted that normal fat turnover is continuous and that, although the human turnover rate is unknown, the turnover rate in the rat is just 6 days. This process can free up unbound DDT, which will then circulate in the blood:

The functions bearing directly on the mobilization and deposition of fat appear to be a continuous process. Complete fat turnover in the mouse on a constant diet is estimated to require six days. The turnover in man is probably slower, because his metabolic rate is lower; it most likely varies within wide limits and must be greatly accelerated under conditions that make demands on the fat reserve... It appears to be a reasonable assumption that adipose tissue, which has these many important functions, can be influenced by the presence of cumulative poisons such as the chlorinated hydrocarbon insecticides. Among the more important of these materials are dichlorodiphenyltrichloroethane (DDT)... ”

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The AMA highlighted the fact that DDT is a proven “biological magnifier” with major implications because DDT continually builds up in adipose tissue and can insidiously target important cardiac enzymes and alter the metabolic activity of the adipose tissue itself:

The accumulation of dichlorodiphenyltrichloroethane in fat tissue has been studied extensively, and it has been shown that this tissue acts as a biologic magnifier for the insecticide. The ingestion of minute amounts of dichlorodiphenyltrichloroethane (about 1 part per million) in the diet of rats over a period of time causes accumulation in the fat which can be as high as 30 times the level of intake. It has been demonstrated that dichlorodiphenyltrichloroethane concentrations of 3 to 30 parts per million in the substrate inhibit rat heart cytochrome oxidase. It is possible that this deposited DDT can influence enzymatic activity in adipose tissue.

The AMA also directly linked bioaccumulation to toxicity, stating that increasing lipid solubility increases toxicity:

Perhaps a better indication of the influence of a poison that is retained in the fat is the comparison of the effects of the four principal isomers of benzene hexachloride. If the degree or retention of gamma isomer in fatty tissue is assigned the value of 1, then alpha is rated as 2, beta as 10 and delta less than 1. Chronic effects of these isomers, when fed to rats, can be observed with 100 parts of gamma per million in the diet, 50 of alpha, 10 of beta and about 800 of delta. The direct relation between retention and chronic toxicity appears obvious.

Additionally, the AMA highlighted an often-ignored fact about lipophilic chemical compounds. While scientists at this time had reached consensus that DDT bioaccumulation and biomagnification occurred in fat tissue, little thought had been given to the fact that every cell in the body has a membrane that is rich in lipids. When DDT dissolves in cell membranes, DDT can disrupt the very fine balance of cellular transport; transplacental transport in the developing fetus would be a major concern.

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In fact, dichlorodiphenyltrichloroethane is found in all other tissues in proportion to their fat content. Fats and lipids are constituents of cell membranes and are concerned with the phenomena of cell permeability and cell organization in every tissue of the body...Also, embryonic fat cells have a great capacity for synthesis of cholesterol. The importance of cholesterol in the formation of vitamins and hormones is well established. Consequently, storage of a toxicant in the fat of parenchymal cells is essentially storage in the cell itself, where such important enzymatic processes as oxidation, phosphorylation and cholesterol synthesis take place. The fact that TDE specifically affects the adrenal cortex of the dog gives credence to this postulation.

Finally, the AMA pointed to the properties of all lipid-soluble stable chlorinated hydrocarbons as the overriding threats to human health and the body's homeostatic mechanisms. In other words, the toxicity was not "chemical-specific," and if other compounds (such as PCBs) shared the physical property of fat solubility, they would be expected to be equally toxic.

At present, compounds of the chlorinated hydrocarbon group of insecticides that are fat soluble and chemically stable appear to be readily retained in adipose tissue. Such compounds possess a high order of chronic toxicity, and it is believed that at least part of these effects may be due to the adverse influence the chemicals have on important functions of adipose tissue.

In 1955, a very important presentation was given at the AAAS meeting by Hayes et al. (the report was published in 1956) entitled, "The Effect of Known Repeated Oral Doses of Chlorophenothane (DDT) in Man." [118] Because previous animal studies had shown consistent but variable DDT bioaccumulation, Hayes et al. concluded it was necessary to confirm the effects of human exposures by directly exposing humans in a controlled feeding experiment and measuring DDT in biopsied fat tissue. This was a very unique set of experiments because humans were used as the "animal" and were knowingly exposed to a confirmed toxic compound:

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Much knowledge is available regarding the effect of repeated doses of chlorophenothane (DDT) on a variety of animals. Significant interspecies variation has been found in its toxicity when given orally, the storage of DDT in fat, and the conversion of DDT to 1,1,-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE). Some other aspects of the pharmacology of DDT have not been investigated sufficiently to determine whether interspecies differences are present. A final evaluation of the effect of DDT on man must be made with human subjects. The practical importance of the problem is evident from the fact that a greater tonnage of DDT than of any other insecticide is used in agriculture, that DDT occurs regularly in prepared meals, and that it is stored in the fat of most persons in the general population.

They stated that DDT was then known to have bioaccumulated “in most of the persons in the general population.” This statement is extremely important and noteworthy for this case because Hayes et al. predicted bioaccumulation based on just two facts: 1) DDT’s high lipid solubility had resulted in rapid and high bioaccumulation animals and livestock; and 2) a great “tonnage” of DDT had been released into the environment. Despite having no more information than these two facts, Hayes et al. felt comfortable about this prediction that the “general population” had accumulated DDT.

The Hayes et al. experiments[118]⁸ (started in 1954) were conducted on human male prison volunteers in which each man was given a daily dose of 3.5 or 35 mg DDT in various emulsions for periods of up to 18 months. At the end of the prescribed interval of an exposure, a small incision was made in the abdomen, a biopsy specimen of abdominal fat was removed, and the DDT content was measured. As noted earlier, the U.S. food supply was known to be contaminated, so adjustments were made for both DDT and DDE residue concentrations detected in the typical prison meal.

Based on their graphs, Hayes et al. stated, “It is clear that storage was directly proportional to dosage. The graphs suggest that, at the dosages used, human males achieve storage equilibrium for DDT in about a year, but further observation is necessary to establish this.” DDT had

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bioaccumulated to significant levels even at low levels of exposure and that it was biomagnified. For example a DDT dose of 3.5 mg resulted in fat concentrations of 354 mg and 613 mg after approximately 6- and 12-month exposures, respectively. As the apex receptor in the food chain, humans unknowingly accumulate chlorinated compounds released into the environment to significant levels.

8.4. In the 1960s, DDT and PCBs were known to be ubiquitous and bioaccumulative

If PCBs had been substituted for DDT by investigators in each of the above-summarized studies, the results would have been roughly the same. As producers of both PCBs and DDT, Monsanto must have known that both compounds shared very similar lipid solubility properties and, therefore, should have known that all of the DDT studies pertained to PCBs as well. This proposition is supported by the testimony of Monsanto's corporate representative.¹⁸

By the 1960s, the full realization of the massive historical uncontrolled releases of both DDT and PCBs came into sharp focus. Detailed food residue measurements were made of these two highly lipid-soluble compounds in different categories of food products, confirming that the U.S. food supply was highly contaminated and that the general public had likely been unknowingly consuming DDT and PCBs for many years prior. Starting in 1969, the FDA began monitoring PCBs in a variety of foods and could then determine the amount of PCBs in the total U.S. diet; from this information, FDA could calculate the daily human PCB intake.[119]

In 1975, at the National Conference on Polychlorinated Biphenyls (sponsored by the U.S. EPA), Drs. Jelinek and Corneliussen (Director of the Division of Chemical Technology, Bureau of Foods, Food and Drug Administration and Assistant to the Director of the Division of Chemical Technology, Bureau of Foods, respectively) presented "Levels of PCBs in The U.S. Food Supply." [119]

¹⁸ Kaley Deposition, Colella v. Monsanto, 11/17/2011, pages 34-44.

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From the amount of PCB contamination measured in each food commodity, the authors calculated the average daily intake for a typical diet, which they termed the “Total Diet.” It should be stressed that 50% of this population would have higher daily intakes. Jelinek and Corneliussen noted that they could look at the multiyear survey results and identify patterns of foods contaminated with the highest levels of PCBs and make the following broad generalization by 1975:

In summary, the breadth of occurrence of PCB's has narrowed to the point where freshwater fish are now the primary source of PCB's in our diet. Thus, the daily PCB intake for the average citizen is low, since his consumption of freshwater fish is low, and even here, most of the commercial freshwater fish contain less than 5 ppm PCBs. However, the estimated intake of the average consumer is only a guidepost, and the Food and Drug Administration must consider the dietary consumption patterns of significant sectors of the population which are significantly different from the average. For example, PCB intake could be quite different for those people whose diets include substantial quantities of sports fish.

Because fish was the food commodity exhibiting the highest PCB contaminant levels, Jelinek and Corneliussen stated that the focus should be on preventing PCBs from entering and contaminating the aquatic environment:

For the future...means must be employed by the responsible Federal and State agencies to effectively halt the entry of PCB's into the aquatic environment.

It wasn't until the early 1970s that routine biomonitoring of the U.S. general population was conducted to determine the body burdens for many environmental pollutants among the U.S. general population. In 1967, the Human Monitoring Survey was established by the Pesticides Program of the U.S. Department of Health, Education, and Welfare. In 1970, (the first year the EPA was established as an Agency), EPA began measuring DDT and, later in 1972, PCBs in fat tissue as part of its National Human Monitoring program. In these early biomonitoring studies, both DDT and PCBs were detected in the general population.[120]

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Although the extent of PCB contamination was not widely studied until the late 1960s and 1970s, it is my opinion that Monsanto had all the facts necessary to know PCBs as bioaccumulative, ubiquitous environmental contaminants much earlier. This opinion is supported by a memo developed by a consultant (Dr. Robert Metcalf) for Monsanto in 1969.[121] At the time, Metcalf was a professor at Illinois University and one of Monsanto's scientific consultants. In 1969, he wrote an internal memo to Monsanto titled, "Report and Comments on Meeting on Chlorinated Biphenyls in the Environment at Industrial Biotest Laboratories, Chicago, March 21." In this memo, he considered whether it is possible that the massive amounts of PCBs Monsanto had produced over decades could have resulted in worldwide pollution. His conclusion was a simple yes. What is striking about Metcalf's conclusion is that it was based on a few specific long-known facts and scientific principles: Monsanto produced massive amounts of PCB over 40 years; tens of millions of pounds of PCBs were used in applications where PCBs "must escape into the environment;" PCBs are stable and environmentally persistent; and both PCBs and DDT are lipid soluble and water insoluble, and had been produced in roughly the same amounts over decades. Metcalf's conclusions did not require the development of any new technology or scientific discoveries—the stated bases for his conclusions were available to Monsanto decades before.

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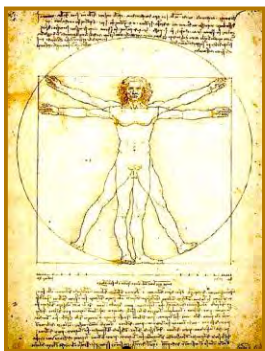
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Courses: Environmental Risk Assessment (2006-Current)

Environmental Epidemiology (2008-Current)

Toxicology (2016-Current)

University of Colorado Medical School, School of Pharmacy, Adjoint Professor

Course: Risk Assessment and Toxicology (May 1998-2009)

Naval Civil Engineer Corps Officers School, Port Hueneme, California

Courses: Human Health Risk Assessment and Management (1996-2002)

Environmental Statistics (1996-2002)

PROFESSIONAL POSITIONS

Scientia Veritas, L.L.P.

Evergreen, Colorado

President and Principal Toxicologist

March 1997-Current

Terranext

Lakewood, Colorado

Corporate Director of Medical Toxicology and Health Sciences and Principal Toxicologist

November 1996-March 1997

GeoTrans Inc.

Boulder, Colorado

Director of Toxicology and Risk Assessment and Principal Toxicologist

February 1996-November 1996

PRC Environmental Management Inc.

Denver, Colorado

Toxicology and Atmospheric Science Discipline Leader and Principal Toxicologist

February 1992-November 1995

PTI Inc.

Boulder, Colorado

Senior Toxicologist

May 1991-February 1992

EPA Neurotoxicology Division

Research Triangle Park, North Carolina

Consulting Toxicologist

1984-1986

University of Michigan School of Public Health, Department of Industrial and Environmental Health

Ann Arbor, Michigan

Consulting Toxicologist and Research Assistant

1980-1986

University of Michigan School of Public Health, Department of Water Quality

Ann Arbor, Michigan

1978-1980

Research Assistant

PROFESSIONAL SOCIETIES/ASSOCIATIONS

Society of Toxicology

Society for Risk Analysis

Society of Environmental Toxicology and Chemistry

American Society for the Advancement of Science

American Chemical Society

PROFESSIONAL EXPERIENCE

EXPERTISE OVERVIEW

Dr. Richard DeGrandchamp has been a practicing toxicologist for more than 33 years. During this time, he has served in the U.S. Department of Justice's (DOJ) Expert Witness Unit and testified in numerous high-profile trials involving environmental contamination in which the judgment awards totaled more than \$20 billion. Dr. DeGrandchamp provides expert witness testimony to DOJ on risk assessment, chemical injury, and toxicology. He has also testified as the toxicologist

expert witness in numerous toxic tort lawsuits that focused on cancer-causing environmental toxicants. He has held a faculty appointment in the Graduate Faculty Program at the University of Colorado Denver/Anschutz Medical Campus for more than 15 years. Dr. DeGrandchamp has served on numerous scientific review panels and has been a toxicological consultant for the U.S. Environmental Protection Agency (U.S. EPA); Department of the Navy (DON); Department of Energy (DOE); Department of Defense (DOD); Massachusetts Department of Environmental Protection (MDEP); Michigan Department of Environmental Quality (MDEQ); District of Columbia's District Department of the Environment (DDOE); and many chemical, pharmaceutical, and manufacturing companies. He has conducted or directed more than 300 human health risk assessments regulated under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; Superfund); Resource Conservation and Recovery Act (RCRA); and Underground Storage Tank (UST) programs. He has been the lead negotiator in over 150 regulatory meetings and provides expert toxicological support, as well as expert witness testimony, on all issues related to toxic chemical exposure. Dr. DeGrandchamp has provided expert toxicological legal support in the private sector and U.S. EPA Regions 3, 5 and 8 in environmental cases involving RCRA and CERCLA hazardous sites. He has been a member of numerous expert scientific panels and authored many risk assessment, statistical, and toxicological guidance documents for U.S. EPA and DOD.

FACULTY APPOINTMENTS

Dr. DeGrandchamp holds a faculty appointment in the Graduate Program at the University of Colorado Denver/Anschutz Medical Campus where he is the lecturer and course director for three courses: Human Health Risk Assessment, Toxicology, and Environmental Epidemiology for the M.S. and Ph.D. program.

Dr. DeGrandchamp also taught human health risk assessment and toxicology courses at the University of Colorado Medical School, School of Pharmacy, where he was responsible for training students in the Ph.D. Toxicology Program.

Dr. DeGrandchamp was a faculty member and instructor at the Naval Civil Engineering Corps Officers School (CECOS), Port Hueneme, California. He developed the first courses for human health risk assessment, toxicology, and risk management.

Dr. DeGrandchamp has developed and presented a hands-on training, three-day toxicology/risk assessment workshop to risk assessors, physicians, and industrial hygienists at the Navy Environmental Health Center (NEHC), Bureau of Medicine, in Norfolk, Virginia.

Dr. DeGrandchamp has instructed many U.S. EPA CERCLA and RCRA personnel, and Navy project managers, in the practice and application of risk assessment, statistics, and toxicology at petroleum-contaminated sites.

LITIGATION EXPERTISE

Dr. DeGrandchamp has been retained as an expert toxicologist to evaluate the cause of death of a 14 male adult. This individual suffered acute and severe clonic-toxic seizures triggered by numerous prescribed medications to control his seizures. Dr. DeGrandchamp is investigating the cause of death. He has been tasked with evaluating the toxicity and synergistic effects of the prescribed medications by the attending physician and how the nursing personnel administered the drugs. He is also determining if his non-prescribed drugs that led to his emergency admission could have contributed to his death and he is reviewing all medical records and hospital treatment to determine and explain the how the child died.

Dr. DeGrandchamp has been retained as toxicological expert consultant for a case involving a pesticide (pyrethroid) exposure that resulted in a 6th month old infant developing severe tonic clonic seizures. He was asked to provide a review of the available medical toxicology information for the pesticide as well as the patient medical records to form an opinion about whether the medical treatment he received during his hospitalization the prescribed medications were correctly administered. He has been tasked with identifying the initial triggering cause and the subsequent toxicological sequelae that

have now triggered nearly 1,000 seizures per day and resulted in severe impairment of cognitive development.

Dr. DeGrandchamp has been retained as an expert for a case involving PFAS contamination and exposure to residents. He will be testifying on all issues relating to PFAS toxicity and epidemiology studies in a large cohort (approximately 30,000 residents) that have been exposed to PFAS over the last 4 decades.

Dr. DeGrandchamp has been retained as an expert for a PCB case involving contaminated fish. He will be testifying on all issues relating to the human health risks and toxicology of PCB ingestion at different transects of a major river that encompasses areas of fishing.

Dr. DeGrandchamp has been retained as an expert for a polluted site where PFAS was manufactured and have been released into a river that serves as a drinking water source for hundreds of thousands of residents. This group of toxic chemical compounds includes PFOA, PFOS, as well as more recently manufactured compounds that were specifically developed to replace the highly toxic PFAS compounds (including GenX, and Nafion-117) that are no longer produced in the U.S. He has been tasked with forming an opinion about the individual and collective toxicity of these compounds to the exposed population. He is responsible for reviewing company documents that include operation history and numerous toxicity studies.

Dr. DeGrandchamp is an expert witness for a toxic-tort lawsuit. He will be testifying that decades of exposure to PCBs caused diverse and severe health effects in a tribe that was exposed to PCBs over 4 decades. He is responsible for evaluating the fingerprint from multiple sources and linking those to blood samples for the cohort. He will be evaluating specific PCB congeners based on body burden studies and show they are specifically associated with non-cancer health effects based on a series of epidemiology studies. He will also be conducting an epidemiology study of cancers in the cohort to determine if those PCBs are also associated with an elevated risk of cancer.

Dr. DeGrandchamp is an expert witness for a coal-burning facility that has generated numerous heavy metals that have contaminated numerous properties near the facility. He is responsible for evaluating the regional distribution of centrospheres, that serve as indicator particles, to first identify the extent of the regional contamination and then to evaluate the heavy metal contamination associated with those particles to determine if the level of those metals pose a risk to the community.

Dr. DeGrandchamp is an expert witness for a PCB site, where PCBs have been historically released for more than four decades to determine the sources of those PCBs as a foundation to identify localized releases of Potentially Responsible Parties. He will be determining the extent of regional Natural Resources damages for purposes of liability and to support extensive cleanup.

Dr. DeGrandchamp recently completed testifying in a series of toxic tort lawsuits suits that culminated in a jury award of \$46 million for three Non-Hodgkin Lymphoma (NHL) patients. During these trials, his testimony on the history of cancer testing demonstrated Monsanto could have and should have conducted cancer studies back in the 1930s and that those studies would have clearly shown PCBs were carcinogenic, which could have prevented widespread PCB environmental contamination that then ultimately led to contamination of the U.S. food supply over an 80-year period. He showed that while hundreds of other synthetic chemicals resembling PCBs had been tested for carcinogenicity by 1940, Monsanto took no steps to conduct any cancer study until the 1960s. He also provided testimony that linked PCB-body burden with NHL, which was necessary to prove Monsanto's PCBs "caused" NHL. For this part of his testimony, Dr. DeGrandchamp showed that the complex molecular events triggered by PCBs cause specific genetic lesions at locations in the DNA, triggering a cascade of events that result in NHL (summary available at <http://verdictsearch.com/verdict/monsanto-to-blame-for-pcb-exposure-cancer-suit-argued/>; <http://www.ecowatch.com/monsanto-ordered-to-pay-46-5-million-in-pcb-lawsuit-in-rare-win-for-pl-1891143419.html>). This verdict subsequently triggered settlement discussions (reported to be \$280 million) that are underway between the hundreds of remaining NHL patients and Monsanto.

Dr. DeGrandchamp is the expert witness for plaintiffs in the Blackwell Zinc Smelter lawsuit alleging property damages due to lead, arsenic, and cadmium contamination of more than 200 properties in Blackwell, Oklahoma. He is responsible

for conducting risk assessments to determine the effects of contaminants on the central nervous systems of the Blackwell children living on contaminated Blackwell properties.

Dr. DeGrandchamp was the DOJ expert in toxicology in the British Petroleum (BP) Deep Water Horizon oil spill in the Gulf of Mexico case that was settled last year for \$20 billion (case summary available at: <https://www.justice.gov/enrd/deepwater-horizon>). He was responsible for conducting toxicological evaluations, epidemiology studies, and risk assessment to assess the potential health threats to more than 40,000 cleanup workers and shoreline residents living in Louisiana, Florida, and Alabama.

Dr. DeGrandchamp was the expert consultant to the U.S. Department of Justice providing toxicology and risk assessment support on a coke/steel manufacturing operation site in West Virginia. He was responsible for assessing human health risks to children living off site in a residential area and at their schools. He determined that the cancer and noncancer risks were unacceptable based on recent EPA air monitoring data collected at nearby schools. Dr. DeGrandchamp applied EPA guidance for early lifetime exposures for coke-related contaminants that are mutagenic. He also conducted an epidemiological evaluation and determined that the residential population was at risk for a wide range of medical conditions.

Dr. DeGrandchamp was an expert consultant to DOJ on the Centredale Manor Superfund site in Rhode Island. This complex site was highly contaminated with dioxins, PCBs, and heavy metals. DOJ was awarded \$104 million, and a case summary is available at <https://www.epa.gov/enforcement/case-summary-epa-issues-104-million-order-cleanup-work-centredale-manor-superfund-site>.

Dr. DeGrandchamp was retained as an expert witness in a toxic tort suit involving a wrongful death associated with exposure to cleaning solutions. He was responsible for evaluating all medical records and the death certificate to determine whether the cause of death was related to an acute exposure.

Dr. DeGrandchamp was an expert witness for the District of Columbia's Department of the Environment and D.C. Attorney General's office in a case involving vapor intrusion into approximately 500 homes in Washington D.C. due to gasoline and chlorinated solvents (PERC). For this site, he conducted more than 1,500 individual risk assessments for each of the sites to identify specific homes where the contaminants could trigger medical conditions and/or cancer and made the necessary toxicological/dosimetric adjustments to EPA toxicity values for early life exposures and individuals with preexisting medical conditions. This study was used to determine which homes required vapor mitigation to reduce indoor contaminants to acceptable levels. Dr. DeGrandchamp also conducted a newly developed forensic statistical approach to determine the responsible contaminant sources.

Dr. DeGrandchamp served as the toxicological expert for the Navy Office of General Council and the Navy Environmental Health Center, Bureau of Medicine, in a toxic tort suit filed by more than 6,000 residents on the Island of Vieques. He evaluated the plaintiffs' claims alleging long-term toxic exposures due to Navy activities on the island over a 60-year period associated with bombing exercises resulted in wide-ranging medical conditions. Damages were set at more than \$1 billion. Dr. DeGrandchamp was responsible for analyzing hundreds of historical documents, medical records, and biological hair samples. Additionally, he was responsible for analyzing biological samples to determine the current levels of toxic metal exposures to distinguish between background and military-related exposures, as well as conducting an epidemiological study to verify cancer rates, which were then compared with the current cancer registry.

Dr. DeGrandchamp was an expert witness providing toxicological expertise to DOJ and EPA Region 3 on the Metal Bank Superfund Site in Pennsylvania, which was contaminated with PCBs and dioxins. He provided expert reports, rebuttal reports, supplemental reports, depositions, and interrogatories, and assisted DOJ in preparing for depositions. Ultimately, the court ruled in DOJ's favor, deferring to Dr. DeGrandchamp's expert opinion regarding the level of contamination and associated human health risks. He also provided supporting risk assessments in the second phase of the trial, where he developed a risk-based remedial strategy for mitigating risks to acceptable levels. A summary of the approximate \$30 million settlement is available at <https://www.paed.uscourts.gov/documents/opinions/03D0023P.pdf>

Dr. DeGrandchamp was an expert witness for DOJ in a bankruptcy trial for three hazardous waste sites in Pennsylvania. He

was responsible for conducting a toxicological assessment of potential risk associated with exposure to PCBs and to address the question of whether it was necessary to secure the funds for future remediation. The court ruled for DOJ and required that \$15 million be secured for additional studies and remediation.

Dr. DeGrandchamp was an expert witness for DOJ and EPA Region 8 involving PCBs and dioxins at the U.S. Magnesium Corporation (MagCorp) Superfund Site in Utah. He was responsible for conducting a comprehensive toxicological evaluation of workers' health and exposure conditions based on their occupational responsibilities within the plant. He collaborated with Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), and EPA toxicologists and physicians to design and implement a medical surveillance program in which blood samples and employee coveralls were collected to determine the extent of dioxin and PCB exposure. Based on the blood sample data, Dr. DeGrandchamp was able to identify high-risk workers and submit a worker protection plan to attenuate exposures. He also used the dioxin levels measured in their contaminated work coveralls to show they were exposing family members to high cancer risk and reproductive effects. This analysis proved that they were unknowingly engaging in the well-known phenomenon of "Fouling Their Own Nests" and provided the basis for developing a worker and family protection plan.

Dr. DeGrandchamp served as the expert toxicologist for U.S. DOJ and U.S. EPA Region 5 in a case against a steel manufacturing facility in Ohio. He was responsible for conducting toxicological evaluations for residents who lived near the AK Steel Superfund Site and had been eating PCB-contaminated fish caught in a nearby river. Upon completion of expert reports, a settlement was reached for approximately \$25 million. A description is available at https://www.justice.gov/archive/opa/pr/2006/April/06_enrd_200.html.

Dr. DeGrandchamp has provided expert testimony in several toxic tort litigation cases for a potentially responsible party at a chrome-plating facility in Texas. His responsibilities included reviewing medical records, preparing pretrial reports, giving depositions, presentations during arbitration and mediations, and preparing guardian *ad litem* documents.

Dr. DeGrandchamp has worked extensively with U.S. Navy attorneys on diverse health and environmental issues. Dr. DeGrandchamp provided toxicological expertise and negotiation support in the Navy CLEAN program. He was a member of a multifaceted installation wide technical panel that evaluated the legal basis for developing innovative remediation strategies to streamline the CERCLA process for all Navy bases scheduled for closure or transfer. He prepared position papers; developed the Navy's overall remediation strategy; and negotiated with local, state, and federal regulatory agencies. He was the technical expert in numerous negotiations and dispute resolution meetings.

Dr. DeGrandchamp served as the toxicological expert in a toxic tort case filed against a major pesticide manufacturer that involved domestic exposure to a pyrethroid pesticide. He prepared an expert report that was successfully used to have the case dismissed.

Dr. DeGrandchamp provided litigation support for a toxic tort case involving a PRP in Montana involving exposure to petroleum constituents. His responsibilities included developing the overall scientific strategy and designing a sampling plan for the defense.

Dr. DeGrandchamp provided legal support for a chlorinated solvent site in Montana. He also served as the technical advisor on community relations for this project. He was responsible for interacting with the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR).

SUMMARY OF PROJECT EXPERIENCE

Under Dr. DeGrandchamp's direction, SV was awarded a sole source contract to provide expert consulting services to the Michigan Department of Environmental Quality (MDEQ). Dr. DeGrandchamp provided toxicological, risk assessment, and negotiation support to MDEQ regarding perfluorinated chemical (PFCs) contamination of Wurtsmith Air Force Base groundwater that migrated offsite to the Au Sable River, where it has contaminated fish. Dr. DeGrandchamp conducted a literature review of PFC information; prepared a report summarizing findings of the literature search; conducted a site-

specific review and analysis of PFC data from the Wurtsmith site; performed a comparison of exposure and general media contaminant levels at other sites (nationally and worldwide); analyzed the potential risks to humans and ecosystems in and around the Wurtsmith site; provided a report on the site-specific review and analysis; provided an analysis of Air Force responsibilities in relation to CERCLA and other environmental and human health regulations; proposed additional work at the Wurtsmith site by the Air Force, MDEQ, and/or EPA necessary to identify risks, actual human health impacts and ecological impacts, as appropriate; summarized this analysis into a report of additional responsibilities; and traveled to Michigan to meet with personnel from MDEQ and the Air Force.

The PFCs are the result of firefighting training activities at Wurtsmith, and Dr. DeGrandchamp provided support to MDEQ in working with EPA Region 5 and the U.S. Air Force. PFCs constitute an emerging group of highly toxic chemicals of concern (COCs) and Dr. DeGrandchamp was charged with developing toxicity values. SV was also contracted to work on the project because of Dr. DeGrandchamp's previous experience working on Air Force projects. Dr. DeGrandchamp aided the state of Michigan in connecting with the proper Air Force personnel in order to secure funding for future studies and in pointing out to all parties the benefits of conducting such work before any potential property transfers or re-use plans are implemented.

Under Dr. DeGrandchamp's direction, SV was awarded a sole source contract with the District of Columbia Department of the Environment and is currently providing oversight for all risk assessments at the Washington Navy Yard in D.C., which has been in continuous operation for 200 years. He is responsible for evaluating the public health threats from contaminants on the base, as well as releases into the Anacostia River. He is currently conducting a forensic analysis of PCBs and dioxins that will be used to forensically "fingerprint" different sources of contamination in the river.

Dr. DeGrandchamp conducted a time-critical toxicological evaluation of children in a daycare facility in the District of Columbia that resulted in an emergency evacuation of children from the daycare. His analysis showed vapor levels had reached neurotoxic levels, which required evacuation until vapor mitigation systems could be installed.

Dr. DeGrandchamp prepared toxicological support for new regulations for exposure to toxic chemicals bacteria, viruses, and protozoa in stormwater reuse in D.C. The approach combines the risk assessment approach developed by U.S. EPA and the World Health Organization's disability-adjusted lifetime years (DALY).

Dr. DeGrandchamp was retained to provide expert witness testimony in a toxic tort suit involving a death from phosphoric acid inhalation. Responsibilities included evaluating epidemiological/toxicological published studies to derive the plausible lethal dose, reconstructing possible exposure dose, reviewing medical records to evaluate etiology of illness and symptoms leading to death, and a critique of the coroner's report.

Dr. DeGrandchamp has developed new toxicity values for DON for chemicals did not have U.S. EPA-verified toxicity values. To date, he has developed toxicity values for more than 95 chemicals.

Dr. DeGrandchamp routinely conducts toxicological reviews to determine if U.S. EPA-toxicity values need to be modified or updated based on new toxicological studies.

Dr. DeGrandchamp prepared a comprehensive guidance document on sampling and analysis, and conducting risk assessments at PCB- and dioxin-contaminated sites for DOD. These documents were used to train Navy personnel in the environmental restoration program who are responsible for remediating Navy installations that will be returned to civilian use.

Dr. DeGrandchamp conducted a geostatistical analysis of background conditions for dioxin, furans, and PCBs for the Rocky Mountain Front Range for EPA Region 8. This analysis was based on a new statistical method he developed based on geochemical analyses using linear regression and principal component analysis.

Dr. DeGrandchamp developed and negotiated a geochemical method for evaluating background conditions in the state of Florida for the Department of Defense (Navy). After conducting a pilot study to demonstrate that the geochemical technique could be used to define background conditions and identify chemical release areas, the Florida Department of Environmental Protection (FDEP) formally approved the technique for use on Superfund and Federal Facilities throughout Florida.

Dr. DeGrandchamp conducted a toxicological evaluation of chemicals detected at Naval Air Station (NAS) Atsugi in Japan for the Department of the Navy. This project involved developing new toxicity values for unique chemicals and their breakdown products. This was a sole source contract resulting from specific recommendations by the National Academy of Sciences and the Navy Surgeon General. Ultimately, Dr. DeGrandchamp used these toxicity values to show that contaminant levels did not pose risks to Japanese citizens.

Dr. DeGrandchamp was selected by U.S. EPA to serve on an expert External Peer Review Panel to provide technical oversight for *Draft Human Health Risk Assessment Protocols for Hazardous Waste Combustion Facilities and Screening Level Ecological Risk Assessment Protocols for Hazardous Waste Combustion Facilities*. He was responsible for providing expertise in risk assessment and toxicology on the panel and participated in a two-day public hearing/workshop to field and respond to public comments prior to finalization and release of the guidance.

Dr. DeGrandchamp served as the Technical Lead for EPA Region 6 in developing a new technical guidance document for RCRA sites: *Risk Management Strategy*. He was responsible for all technical sections and responding to public comments.

Dr. DeGrandchamp served as an Expert Consultant to Booz Allen for a project involving asbestos-containing materials (ACMs) at Lowry AFB in Colorado. His responsibilities included researching technical and legal precedence for sampling ACM in soil; reviewing Air Force ACM sampling work plans for substance and approach; identifying potential legal liabilities pertaining to ACM issues; outlining ACM health risk scenarios; and recommending a path forward for ACM sampling and remedial activities for the Air Force at Lowry AFB, Colorado. In the course of this work, Dr. DeGrandchamp conducted surveys and pattern analysis of surface soil; attended meetings/negotiations with CDPHE; provided legal non-testifying expert support to Air Force attorneys; developed sampling and analysis plans for contaminated areas and activity-based sampling; conducted statistical analysis on areas of concern; developed risk management protocols and evaluated several novel approaches based on new analytical procedures to expedite decision-making; conducted field investigations; reviewed extensive epidemiological studies to evaluate toxicological endpoints; and calculated health risks and prepared risk assessment reports.

Dr. DeGrandchamp provided EPA Region 8 with toxicological and risk assessment technical support at two RCRA sites involving hazardous solvent exposure to off-site residents. He was responsible for evaluating risks and health hazards associated with vapor entering homes from contaminated groundwater into nearby homes. He was responsible for evaluating current toxicological peer-reviewed toxicological studies on formaldehyde to identify health problems among residents, determine acceptable levels of exposure, and identify homes that may require interim measures or evacuation of residents.

Dr. DeGrandchamp conducted a background analysis implementing *Procedural Guidance for Statistically Analyzing Environmental Background Data*, which he authored for the Navy, at NAS Whiting (Milton Florida). This approach was then used to identify chemicals of concern for risk assessment, evaluate Applicable or Relevant and Appropriate Requirements (ARAR), and identify chemical releases. Successful completion of this project was expected to save DOD and the state of Florida \$30 million in potential remediation costs.

Dr. DeGrandchamp conducted a comprehensive review and analysis of diverse scientific methods used to evaluate risks associated with lead exposure for DON. He prepared a Navy position paper that evaluated all lead risk assessment models, including the scientific veracity of the U.S. EPA Integrated Exposure Uptake Biokinetic Model (IEUBK) software code, the California Lead Spread Model, and the probabilistic Integrated Stochastic Model to make recommendations for improvement. He also developed the DON risk assessment strategy to evaluate adult lead exposure in order to expedite lead cleanup at closing Naval installations.

Dr. DeGrandchamp developed a cost-effective, risk-based corrective action (RBCA) approach for a hazardous waste site for Lockheed Martin in Denver, Colorado. The approach incorporated Monte Carlo simulation techniques to accurately estimate actual site-specific risks based on realistic exposures. A cost-benefit matrix was developed to guide risk management decisions.

Dr. DeGrandchamp provided technical expertise on wide-ranging issues to EPA Regions 8 and 6 RCRA and CERCLA programs. He provided toxicological and statistical support on all remedial investigations and feasibility studies conducted

at Rocky Flats Nuclear Weapons Plant (RFP) and was involved in all investigations pertaining to the analysis of human health risks resulting from chemical and radionuclide exposures. He developed data quality objectives and risk assessment methodology, statistical analyses, sampling and analysis plans, and oversaw all chemical and radiological fate and transport modeling. He compiled a database for conducting Monte Carlo simulations and provided technical reviews on supplemental guidance for conducting Monte Carlo simulations for EPA Region 8. He developed a cost-effective risk assessment template for RFP to streamline and provide consistency for all risk assessments. Dr. DeGrandchamp was responsible for evaluating DOE's statistical analyses and risk assessments, and ensured results were consistent with U.S. EPA, the International Commission on Radiation Protection (ICRP), and Nuclear Regulatory Commission (NRC) methodologies. He assisted EPA Region 8 in negotiating numerous disputes and was a participant in a workgroup of nationally recognized experts in binding arbitration involving statistical analyses. He was selected as a member of an interagency committee that included the Colorado Department of Natural Resources, Colorado Department of Health, Colorado Fish and Wildlife Service, EPA Region 8, and DOE to scope, design, and implement a comprehensive, installationwide human health and ecological risk assessment for Rocky Flats.

Dr. DeGrandchamp provided scientific expertise to DOE on toxicological, risk assessment, and statistical issues at the Savannah River Site (SRS) in South Carolina. He reviewed human health risk and dose assessments conducted for numerous operable units and participated on a task force responsible for establishing background conditions. He was invited to lecture on risk assessment and statistical issues by EPA Region 4, DOE, and the South Carolina Department of Health project managers and toxicologists.

Dr. DeGrandchamp conducted numerous baseline risk assessments at NAS Lemoore in California. These risk assessments were ultimately combined into a comprehensive installationwide risk assessment that involved fate and transport modeling of contaminants, coupled with the analysis of current and potential future health risks. He was responsible for all negotiations with federal and state regulators. He successfully negotiated cost-effective management of human health risks during remedy selection by using a risk-based approach to avoid unnecessary and expensive remediation.

Dr. DeGrandchamp conducted all risk assessments and coordinated feasibility studies for NAS Moffett Field in California. He carried out a detailed future land use analysis that was used to focus risk mitigation strategies based on probable future land use. The land use analysis was also used to focus human health risk assessments on realistic exposure conditions to avoid unrealistic conservative default assumptions. He negotiated all aspects of the risk assessment approach with state and federal regulatory agencies. The Navy requested that Dr. DeGrandchamp assist the Department of Justice in averting formal dispute resolution.

Dr. DeGrandchamp conducted risk assessments for NAS Alameda in California. He was responsible for developing the overall risk assessment approach and negotiating all technical aspects of the Navy project with local, state, and federal regulators. He was also tasked with preparing innovative approaches to establish anthropogenic and nonanthropogenic background conditions, preliminary remediation goals, and data aggregation to estimate exposure-point chemical doses. He was also responsible for developing a Navy policy document for risk-based corrective action at petroleum sites.

Dr. DeGrandchamp provided oversight to DOD for risk assessments conducted for NAS China Lake. He was responsible for implementing a risk-based, cost-effective approach for remediation and alternative cleanup levels based on actual site exposures.

Dr. DeGrandchamp provided technical expertise to the Massachusetts Department of Environmental Protection for radionuclide risk assessments, compliance, and cleanup standards. He worked with the state to develop state guidance for radionuclide cleanup of all Department of Defense and Nuclear Regulatory Commission operated sites within the state.

Dr. DeGrandchamp provided EPA Region 8 with technical oversight for all remedial investigations and risk assessments for F.E. Warren Air Force Base in Wyoming and Tooele Army Depot in Utah. He conducted a risk assessment in response to an emergency exposure condition for off-site residents at F.E. Warren AFB who were directly exposed to high concentrations of organic solvents.

Dr. DeGrandchamp led the human health and environmental risk assessment task force for EPA Region 6 in studying

potential adverse health effects associated with emissions from several incinerators in Midlothian, Texas. This investigation was prompted by strong public concern about adverse health effects on humans and livestock. In this evaluation, Dr. DeGrandchamp analyzed the potential for dioxin to produce birth defects, spontaneous abortions, and other potential toxic effects.

Dr. DeGrandchamp investigated the human health risks associated with RCRA facilities in southern California. He conducted the risk assessment for the onsite human receptors, as well as the surrounding community, to determine the potential risks to pregnant women from benzene, arsenic, and cadmium exposure in groundwater. He also evaluated the risks to fetuses via *in utero* exposure. At another RCRA facility, he conducted a risk analysis to determine potential risks associated with arsenic-laden fly ash used as landfill material.

Dr. DeGrandchamp provided oversight and technical support to the EPA Region 8 (Montana office) RCRA division for remediation of oil refineries in Billings, Montana; Mandan, North Dakota; and Commerce City, Colorado. He oversaw all phases of the RCRA process involving preliminary investigations and corrective measures studies. He developed health-protective cleanup levels, and evaluated facility permitting and remediation enforcement. Together with Colorado Department of Health officials, he worked to negotiate remediation goals and a cost settlement.

BIOMEDICAL RESEARCH

Dr. DeGrandchamp investigated the neurotoxic mechanisms associated with exposure to mercury and acrylamide. This information was incorporated into the toxicological database developed by U.S. EPA and the Occupational Safety and Health Administration to set regulations and establish safe exposure conditions for occupational workers.

Dr. DeGrandchamp investigated the neurotoxic effects of alcohol on the developing nervous system, which produces fetal alcohol syndrome. He was responsible for developing new research methodologies and approaches to investigate subtle molecular changes in the nervous system.

Dr. DeGrandchamp designed experimental paradigms to study the bioavailability of mineralogical forms of heavy metals, such as arsenic and cadmium, from mining tailings for a CERCLA site in Montana.

Dr. DeGrandchamp worked on a project for the National Institutes of Health to investigate the neurophysiological mechanisms of strychnine poisoning. In this capacity, he coordinated a team of experts and managed all technical personnel in a multifaceted research program to elucidate the steps that result in central nervous system damage.

Dr. DeGrandchamp further refined the neurotoxic esterase *in vivo* enzyme assay used to evaluate neurotoxic damage resulting from nerve agents and pesticides. This laboratory method has become a standard methodology to screen neurotoxic compounds in the chemical industry and to evaluate the neurotoxic potential of chemical weapons. He also developed a correlative animal model for U.S. EPA to quantify chemical-induced neuropathies associated with exposure to pesticides and nerve agents.

PUBLICATIONS AND POLICY DOCUMENTS

Dr. DeGrandchamp has authored over 100 major toxicological and human health risk assessments that have undergone extensive peer-review. However, many of these reports could not be published due to confidentiality or proprietary information.

1. Delaney, R. and R. L. DeGrandchamp. 2012. *Michigan's Contaminant Induced Human Health Crisis. Addressing Michigan's Future by Facing the Challenge of the Evolving Nature of Environmental Contamination*. August 12, 2012. 93 pages.
2. DeGrandchamp, R. L. 2007. *Expert Report of Dr. Richard L. DeGrandchamp, Ph.D. Regarding the Magnesium Corporation of America, Rowley, Utah*. Prepared for the U. S. Department of Justice, February 6, 2007. 108 pages.

3. DeGrandchamp, R. L. 2005. *Final Standard Operating Procedures: Investigating and Managing Lead Risks at Navy Installations*.
4. Johnston, R. K., S. A. Kurtz, R. L. DeGrandchamp, and M. G. Barron. 2005. *A Guide for Determining the Risk of PCB Exposure to Ecological Receptors. Final Report*. Prepared for Naval Facilities Engineering Command (NAVFAC) Risk Assessment Workgroup, Washington Navy Yard, Washington, D.C.
5. DeGrandchamp, R. L. and M. G. Barron. 2005. *PCB Analysis and Risk Assessment at Navy Installations. Part A: Overview of PCB Mixtures*. <http://web.ead.anl.gov/ecorisk/issue/pdf/PCBAnalysisPartA.pdf>
6. DeGrandchamp, R. L. and M. G. Barron. 2005. *PCB Analysis and Risk Assessment at Navy Installations. Part B: PCB Human Health Risk Assessment*. <http://web.ead.anl.gov/ecorisk/issue/pdf/PCBAnalysisPartB.pdf>
7. DeGrandchamp, R. L. and M. G. Barron. 2005. *PCB Analysis and Risk Assessment at Navy Installations. Part C: PCB Ecological Risk Assessment*. <http://web.ead.anl.gov/ecorisk/issue/pdf/PCBAnalysisPartC.pdf>
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APPENDIX B: MILESTONES IN CANCER STUDIES PERTAINING TO PCBs

- 1775:** First Environmental Cancer Identified
Dr. Percivall Pott identifies a relationship between exposure to chimney soot and the incidence of squamous cell carcinoma of the scrotum among chimney sweeps. This later established the connection between coal tar carcinogens and cancer. His report is the first to clearly link an environmental exposure to the development of cancer, as described in Casarett and Doull. [2]
- 1798:** US Public Health Service Established
Fifth Congress of the United States creates agency that later became the US Public Health Service (US PHS) in 1912. The agency is now known as the US Department of Health, Education and Welfare (<https://www.usphs.gov/aboutus/history.aspx>). [3]
- 1863** Inflammation and Cancer
Dr. Rudolph Virchow identifies white blood cells (leukocytes) in cancerous tissue, making the first connection between inflammation and cancer. Virchow also coins the term *leukemia* and is the first person to describe the excess number of white blood cells in the blood of patients with this disease. PCBs cause immunotoxicity (<https://www.cancer.gov/research/progress/250-years-milestones>). [4]
- 1889** Mitotic Figures Identified in Tumors
Dr. Klebs first identifies mitotic figures in tumors (Triolo 1965). [5]
- 1899** Hyaline Bodies Identified as Cancer Hallmarks in Liver Cancer
Dr. Keen reported his findings of hyaline bodies in liver cells from a tumor mass he removed from a patient. (Triolo 1965). [5]
- 1906** Pure Strains of Laboratory Rats Developed
Wistar Institute Breeds Wistar Rat Strain for Biomedical Studies (Baker et al. 1979). [1]
- 1915:** Additional Strains of Laboratory Rats Developed
Long-Evans Rat strain developed for biomedical studies (Baker et al. 1979). [5]

- 1915** First Carcinogenic Chemical Animal Study
Drs. Yamagiwa and Itchikawa induce skin cancer in rabbits by painting coal tar on their ears, constituting the first experimental animal cancer study. Coal tars provide the starting chemical compounds for chemical industry (Loeb and Harris 2008). [6]
- 1922** First Governmental Cancer Research Center Opens
US Public Health Service establishes a special cancer investigations laboratory at Harvard Medical School (<https://www.usphs.gov/aboutus/history.aspx>). [2]
- 1925** Extensive Pathological “Atlas,” Hallmarks of Cancer Described
Dr. Ludford publishes a lengthy treatise titled, The general and experimental cytology of cancer. The pathological lesions used to identify cancers and establishes mitotic figures as key hallmarks of cancer (Ludford 1925). [7]
- 1925** Last Major Strain of Laboratory Rats Developed Sprague-Dawley Rats bred for laboratory research (Baker et al. 1979). [5]
- 1934** Dow Chemical Company Establishes its Toxicology Laboratory [8]
- 1934** Monsanto Begins Testing for Acute PCB Toxicity
Monsanto toxicity studies determine how much can kill animals and evaluates the acute toxic effects of PCBs. Monsanto does not evaluate chronic toxicity in any study until 1970, when the first long-term rat study is completed (Appendix C).
- 1935** Drs. Sasaki and Yoshida Report on Yoshida’s First Long-Term Animal Cancer Study
Liver tumors were produced in rats by including azo dyes in their diets, as reported by Sasaki and Yoshida (in German, 1935), and then by Loeb and Harris. [6]
- 1935** DuPont Dedicates the Haskell Laboratory
The laboratory was built to conduct toxicity studies to protect the health of workers from toxic new chemical products during their manufacture, as well as public health. Laboratories were designed for biochemistry, pathology, and toxicology, and the laboratory was completed with a full library for studying toxicological problems (JAMA 1935). [9] The stated goal was to “Test Each Product for Safety.” [8]
- 1936** U.S. Public Health Service Recommends Chlorinated Hydrocarbon Manufacturing Be Entirely Enclosed and Recommends Laws Be Passed for Medical Monitoring
Dr. Schwartz, MD, a Senior Surgeon in the U.S. Public Health Service, published a peer-reviewed study detailing the emerging reports of widespread skin diseases

and systemic toxicity among workers who were exposed to chlorinated compounds, including PCBs. He made eight specific recommendations to protect both workers and the general public from exposures (Schwartz 1936). [9]

1937 Mitotic Figures Are Now Routinely in Animal Cancer Studies and Clinical Practice To Identify Tumors

Dr. Casey publishes a study showing that counting the number of mitotic figures in tumors was so established and routine that clinical pathologists and oncologists based their diagnoses and prognoses on this one cancer hallmark. (Casey 1937)

1937 National Cancer Institute created by US Congress

Congress passed the National Cancer Act of 1937 to support for cancer research. The Act established the National Cancer Institute (NCI) as the federal government's primary agency to address research and training needs for the cause, diagnosis, and treatment of cancer (<https://www.cancer.gov/about-nci/overview/history>). [10]

1938: DuPont Publishes First Animal Cancer Study

Dr. Hueper identifies DuPont chemicals (not known to be human carcinogens) based on chemical structural triggers in animal studies and identifies many that are carcinogenic. Hueper identifies additional DuPont chemical candidates based on triggers focusing on structural similarities (Hueper 1938). [11]

1937 First PCB Study Published

Dr. Drinker et al. study shows PCBs are extremely toxic and produce unique pathological lesions in the liver (Drinker et al., 1937). [12]

1938 First Major List of Animal Cancer Studies Published

Drs. Cook and Kennaway publish summaries of chemicals tested for carcinogenicity in chronic animal studies, listing approximately 170 referenced studies (Cook and Kennaway 1938). [12]

1938 Second Study on PCBs Published

Dr. Bennett et al. showed unique pathological lesions in the livers of rats that were caused by PCBs. Hyaline bodies, mitotic figures, and hyperplasia were reported, which are all early hallmarks of cancer. [14]

1938 Dow Chemical Company Completes First Long-Term Animal Carcinogenicity Study [15]

1939 Workplace Exposure PCB Levels Developed

Dr. Drinker et al. published further observations on the possible systemic toxicity of certain of the chlorinated hydrocarbons, with suggestions for permissible concentrations in the air of workrooms (Drinker et al. 1939). [16]

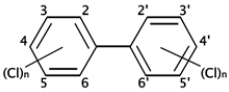
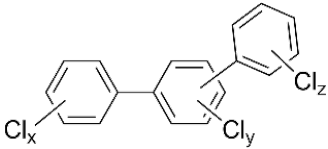
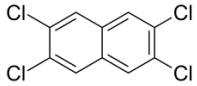
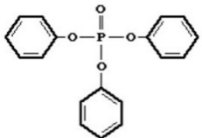
- 1940** Second Major List of Animal Cancer Studies Published
Drs. Cook and Kennaway publish second list of chemicals tested for carcinogenicity in chronic animal studies. The publication lists approximately 480 referenced studies (Cook and Kennaway 1940). [12]
- 1941** Dr. Berenblum First Describes the Molecular Mechanism of Cancer
Cancer studies have advanced to study the mechanism of carcinogenesis using coal tar chemicals. [18]
- 1941** National Cancer Institute Compiles Extensive Compendium of Chemicals Tested in Animal Studies
This summarizes the results of 696 of animal studies focusing on diverse chemicals, identifies 169 carcinogenic chemicals, and includes 1200 references. [19]
- 1944** First Commercial Pure Aroclor Toxicity Study [21]
- 1955** U.S. Public Health Service Publishes Review of the Toxicity of PCBs
Dr. von Oettingen, previously DuPont's first director of the Haskell Laboratories and now the director of the National Institutes of Health, US Department of Health, Education, and Welfare, reviewed the same Drinker studies that I have analyzed and presented his assessment of the toxicity and dangers of PCBs in a book he authored, The Halogenated Hydrocarbons: Toxicity and Potential Dangers. Dr. von Oettingen concluded that PCBs were very toxic and were much more toxic than chlorinated naphthalenes. [21]
- 1966** Widespread PCB Contamination Identified in Sweden
Dr. Jensen reports on widespread PCB contamination in the environment. [22]
- 1968** Yusho Massive PCBs Poisoning in Japan from 1788 People Eating PCB Contaminated Rice
A mass poisoning incident, was caused by ingestion of rice oil that was contaminated with Kanechlor 400, a commercial brand of Japanese PCBs and also contaminated with polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Of the 31 deaths reported, 11 (35.5%) were from neoplasms. Among the Yu-Cheng patients, 24 deaths were reported; half of them were from hepatoma, liver cirrhosis, or liver diseases with hepatomegaly. [24]
- 1970** Monsanto Completes Its First Chronic PCB Study in Rats
The study was conducted by Industrial Bio-Test Laboratories (IBT) and purports to show that PCBs are not carcinogenic, but the studies do not appear to be credible. In reviewing past contract testing work performed by IBT to evaluate the large disparity between IBT's results and other published PCB cancer studies, three IBT scientists were convicted of submitting fraudulent studies to the US

Food and Drug Administration (FDA) in 1993. One of the animal toxicity studies was performed on Monsanto's trichlorocarbanilide ("TCC"), an ingredient in deodorant soaps. (<https://www.courtlistener.com/opinion/460360/united-states-v-moreno-l-keplinger-paul-l-wright-and-james-b-plank/>). IBT prepared three allegedly fraudulent written documents that Monsanto submitted to the FDA. [23]

APPENDIX C: SUMMARY OF MONSANTO

PRODUCT TESTING, 1934-1972

**Exhibit C-1. Chemical Structure Categories:
Polychlorinated Biphenyls and Similar Compounds**

Compound	Chemical Structure
Polychlorinated biphenyls	
Polychlorinated terphenyls	
Polychlorinated naphthalenes	
Pydraul	

**Exhibit C-2. Number of Studies Provided by Monsanto,
by Category and Specific Chemical**

Chemical Category	Number of Studies
Aroclors	
Aroclor 1016	1
Aroclor 1221	8
Aroclor 1232	1
Aroclor 1242	20
Aroclor 1248	4
Aroclor 1254	17
Aroclor 1260	15
Aroclor 1262	3
Aroclor 1268	2
Aroclor 1269	1
Aroclor 1272	1
MCS 1016	6
Total Studies on Chemicals in Category	79
Monsanto Mixtures (Not Pure Biphenyl PCBs)	
5-ring polyphenyl ether product	2
Aroclor 1270 ammonia reaction product	1
Aroclor 2565	1
Aroclor 4273	1
Aroclor 4465	2
Aroclor 5432	1
Aroclor 5442	2
Aroclor 5460	4
Aroclor 6037	1
Aroclor 6040	1
Aroclor 6062	1
Aroclor 6070	1
Aroclor 6090	1
Aroclor Mixture Aroclor/Styrene	3
Aroclor/Halowax Mixtures	4
Chloro Ethyl Benzene	1

Chemical Category	Number of Studies
Chlorinated Styrene	1
DDT	4
FH 145	1
FH-159	1
Inerteen PPO	1
Halowax 1000 (chlorinated naphthalenes)	1
Halowax 1001	1
Halowax 1004	1
Halowax 1014	2
Halowax 1099	3
Hydrolyzed Aroclor 1268	1
MCS-1009	1
MCS-1230	1
MCS-153	1
MCS-295	1
MCS-312	1
MCS-300	1
MCS-395	1
MCS-404	2
MCS-528	2
MCS-90	1
MCS-900	1
MCS-9001	1
MCS-999	1
OS-54	1
OS-57	1
OS-63	1
OS-83	1
OS-95	3
Pydraul	1
Pydraul 135	1
Pydraul 230	1
Pydraul 280	2
Pydraul 281	1
Pydraul 312	1
Pydraul 600	2
Pydraul 625	2
Pydraul AC	2

Chemical Category	Number of Studies
Pydraul F-9	5
Pyranol 1470	1
Santicizer 1706	1
Toxaphene	3
Tricresyl phosphate	1
Total Studies on Chemicals in Category	86
Manuscripts and Memos Not Considered a Study	
Not a study	6
Total Reports in Category (<i>not included in total</i>)	6
Total	165

Exhibit C-3. Toxicological Analysis Studies Conducted by Monsanto Contractors (1934–1972)

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>1. 1934 (0001)</p> <p>REPORT OF DR. FREDERICK B. FLINN OF PATCH TESTS MADE ON MATERIAL RECEIVED FROM SWANN RESEARCH, INC.</p> <p>Dr. Frederick Flynn</p>	<p>Acute dermal patch study with rabbits.</p> <p>Endpoint - dermatitis with short 24 or 48 hr. exposures and 8 tests per solution. 2 week observation.</p>	<p>1. Aroclor 1262: Neg. Rxn.</p> <p>2. Aroclor Mixture Aroclor/Styrene: Neg. Rxn.</p> <p>3. Aroclor Mixture: Aroclors/Styrene: Pos. Rxn</p> <p>4. Aroclor 1248: Pos. Rxn</p> <p>5. Aroclor 1248 "Special": Pos. Rxn.</p> <p>6. Aroclor 1269: Neg. Rxn.</p> <p>7. Aroclor Mixture: Aroclor/Styrene Neg. Rxn.</p> <p>8. Aroclor 1269: Neg. Rxn.</p> <p>9. Aroclor 1269: Neg Rxn.</p> <p>10. Halowax 1000(chlorinated naphthalenes) : Pos. Rxn with ulceration.</p> <p>11. Halowax 1001: Neg. Rxn.</p> <p>12. Halowax 1004: Neg Rxn.</p> <p>13. Styrene Dichloride: Pos. Rxn.</p> <p>14. Aroclor 1248: Pos. Rxn .</p> <p>15. Aroclor 1260: Neg. Rxn.</p> <p>16. Aroclor 1262: Neg. Rxn.</p> <p>17. Chlor Ethyl Benzene: Pos Rxn./Ulceration</p> <p>18. Chlorinated Styrene: Pos Rxn/Ulceration</p>
<p>2. 1937 (0005)</p> <p>THE PROBLEM OF POSSIBLE SYSTEMIC EFFECTS FROM CERTAIN CHLORINATED HYDROCARBONS. Drs. Drinker, Field, Bennett</p>	Discussed in Section 2.	Aroclor/Halowax Mixtures
<p>3. 1938 (0034)</p> <p>MORPHOLOGICAL CHANGES IN THE LIVERS OF RATS RESULTING FROM EXPOSURE TO CERTAIN CHLORINATED HYDROCARBONS. Drs. Bennett, Drinker, Warren</p>	Discussed in Section 2.	Aroclor/Halowax Mixtures
<p>4. 1938 (0061)</p> <p>REPORT TO THE MONSANTO CHEMICAL COMPANY.</p> <p>Dr. Drinker.</p>	Discussed in Section 2.	Aroclor/Halowax Mixtures

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
5. 1938 (0061) REPORT TO THE MONSANTO CHEMICAL COMPANY. Dr. Drinker. Second Report Same Year	Discussed in Section 2.	Not a study. Aroclor/Halowax Mixtures
6. 1938 REPORT TO THE MONSANTO CHEMICAL COMPANY Dr. Drinker.	Discussed in Section 2.	Not a Study. Aroclor/Halowax Mixtures
7. 1939 (0085) FURTHER OBSERVATIONS ON THE POSSIBLE SYSTEMIC TOXICITY OF CERTAIN OF THE CHLORINATED HYDROCARBONS WITH SUGGESTIONS FOR PERMISSIBLE CONCENTRATIONS IN THE AIR OF WORKROOMS. Dr. Drinker	Discussed in Section 2.	Aroclor/Halowax Mixtures
8. 1948 (0091) COVER LETTER: PROJECT W-31 AROCLOR (REPORT ON PATCH TESTING) Dr. Halpern The Barnard Free Skin and Cancer Hospital. <u>One Page</u>	Human screening "Patch Test" Simple test to evaluate if "Aroclors" irritated the skin or caused sensitization from contact with Aroclors. Raw data and details not presented-nevertheless irritation was considered negative. Cohort: 46 volunteers aged 20-53 yrs old 36F/10M ("no negros") . Protocol was very short-term. 24 hr exposure and observed for 48,72 hours for irritation. Repeated 10 days later for "sensitivity."	<u>Not a Study. One-page summary</u> did not identify specific Aroclor. Skin irritation.
9. 1949 (0092) COVER LETTER: PROJECT W-31 AROCLOR (REPORT ON PATCH TESTING) Dr. Halpern, The Barnard Free Skin and Cancer Hospital. <u>Two Pages</u>	Appears to be similar to the study referenced above (1948) with larger cohort (218 v. 46) volunteers. Cohort: 218 aged 20-70 yrs 131F/87M Protocol was very short-term. 24 hr exposure and observed for 48,72 hours for irritation. Repeated 10 days later for sensitivity.	Handwritten note states the Aroclor tested was "1254".

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>10. 1951 (0094)</p> <p>THE MINIMUM LETHAL DOSE OF PYDRAUL F-9 WHEN FED ORALLY TO NEW ZEALAND WHITE RABBITS.</p> <p>Fred Younger, Scientific Associates</p>	<p>Single Minimum Lethal Dose (MLD) study.</p> <p>Determined the acute toxicity from one single high dose.</p> <p>MLD was 0.45–0.67 ml/kg body weight (rabbit) . Interesting that although Aroclors were had been manufactured at this point for ~19 years Monsanto did not conduct a similar MLD study on that group.</p>	<p>Pydraul F-9: Not pure Aroclor</p> <p>Organophosphate with 52.5% Aroclor 1248 added.</p> <p>Single Minimum Lethal Dose (MLD) study.</p> <p>Determined the acute toxicity from one single high dose of Pydraul F-9. The MLD would be classified as very toxic. Death was used as an endpoint and only gross observations of organs were made during necropsy.</p>
<p>11. 1951 (0096)</p> <p>THE MINIMUM LETHAL DOSE OF PYDRAUL F-9 WHEN FED ORALLY TO LABORATORY RATS.</p> <p>Fred Younger, Scientific Associates</p>	<p>Single Minimum Lethal Dose (MLD) study.</p> <p>Determined the acute toxicity from one single high dose.</p> <p>MLD (rat) was 8.4–12.5 ml/kg body weight. This dose is more than 10x higher than previous study with rabbits.</p> <p>One of the key findings was the rats showed severe jaundice with liver damage.</p>	<p>Pydraul F-9: Not pure Aroclor</p> <p>Organophosphate with 52.5% Aroclor 1248 added.</p> <p>Single Minimum Lethal Dose (MLD) study.</p> <p>Determined the acute toxicity from one single high dose of Pydraul F-P</p> <p>MLD was 0.45 and 0.67 ml/kg body weight. Interesting that although Aroclors were had been manufactured at this point for ~19 years Monsanto did not conduct a similar MLD study on that group.</p>
<p>12. 1951 (0098)</p> <p>Letter report to Dr. Kelly from Dr. Halpern, The Barnard Free Skin and Cancer Hospital.</p> <p>Report is illegible, but appears to be a patch test for Pydraul F-9.</p>	<p>Report was illegible.</p>	<p>Pydraul F-9 (?)</p>
<p>13. 1953 (0100)</p> <p>THE TOXICITY OF THE FOGS FORMED BY DROPPING PYDRAUL F-9, AROCLOR 1248 AND TRICRESYL PHOSPHATE, UPON THE SURFACE OF A HEATED INCONEL (PROJECT 49) .</p> <p>Treon, Cleveland, Shaffer, Cappel, Gahegan, Wagner. Kettering Laboratory, University of Cincinnati.</p>	<p>Short term (acute) study of the effects of inhalation when vaporized on inconel tubes heated to extreme conditions. Exposure to Aroclor 1248 caused fatty infiltration and necrosis of liver parenchymal cells. Animals survived exposure to Pydraul F-9 and tricresyl phosphate, but died with Aroclor 1248.</p> <p>Significant differences in toxicological effects between species. Toxic effects were dose related. Skin patch tests were also conducted and showed a dose-dependence mortality ratio of all compounds.</p> <p>MLD of undiluted Pydraul F-9, when maintained in contact with the intact skin of rabbits according to the 24-hr sleeve method of Draize, Woodard and Calvery, was > 3.6 ml/kg and <6.0 ml/kg body weight. Correspond value for tricresyl phosphate was 1.6–2.5 ml/kg. Aroclor 1248 was not lethal at 9.4 ml/kg. Pydraul F-9 and Aroclor 1248 are more toxic if applied to the abraded skin.</p>	<p>Pydraul F-9: Not pure Aroclor: Organophosphate with 52.5% Aroclor 1248 added.</p> <p>Toxicity of Pydraul F-9, “Fogs.”</p> <p>Effects on lung, and liver evaluated. Patch tests also conducted.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>14. 1953 (0182)</p> <p>THE ACUTE ORAL TOXICITY (LD50) OF AROCLOR 1254 FOR RATS.</p> <p>Fred Younger, Scientific Associates.</p>	<p>The purpose of the study was to determine the lethal dose of Aroclor 1254 based on the LD50.</p> <p>It is noteworthy that the "LD50" toxicity test was developed by Bliss in 1939, but Monsanto did not conduct this very basic toxicity study until 1953 which is >20 years after production and use started.</p> <p>The LD50 was determined to be 3.1 ml/kg (rat) .</p>	<p>Aroclor 1254 was used to kill rats. The endpoint was mortality. No cause of death was investigated.</p> <p>Only gross observation was conducted at necropsy. Color change of liver was noted.</p>
<p>15. 1953 (0185)</p> <p>THE ACUTE ORAL TOXICITY (LD50) OF AROCLOR 1242 FOR RATS.</p> <p>Fred Younger, Scientific Associates.</p>	<p>The purpose of the study was to determine the lethal dose of Aroclor 1242 based on the LD50.</p> <p>It is noteworthy that the "LD50" toxicity test was developed by Bliss in 1939, but Monsanto did not conduct this very basic toxicity study until 1953 which is >20 years after production and use started.</p> <p>The LD50 was determined to be 4.15 ml/kg (rat) .</p>	<p>Aroclor 1242 was used to kill rats. The endpoint was mortality. No cause of death was investigated.</p> <p>Only gross observation was conducted at necropsy. Color change of liver was noted-dull red greenish hue. Spleen abnormally dark.</p>
<p>16. 1954 (0188)</p> <p>(A) THE ACUTE ORAL TOXICITY (LD50) OF FUNCTIONAL FLUID OS-54 FOR RATS</p> <p>(B) INHALATION OF OS-54 FUMES BY RABBITS OVER PERIOD OF THREE DAYS</p> <p>(C) OCULAR IRRITATION PRODUCED BY OS-54</p> <p>Fred Younger, Scientific Associates</p>	<p>Acute (LD50) study to determine the lethal dose, eye irritation and inhalation toxicity.</p> <p>Acute oral toxicity (rat) : the LD50 was 13.5 g/kg.</p>	<p>Copy was illegible, but appears to reference OS-54. OS designation appears to indicate it is an aromatic ether not Pure Aroclor</p>
<p>17. 1954 (0194)</p> <p>THE TOXICOLOGICAL INVESTIGATION OF FLUID OS-57</p> <p>Fred Younger, Scientific Associates</p>	<p>Acute oral LD50, dermal lethal dose, eye and skin irritation and inhalation toxicity.</p> <p>The LD50 (rat) could not be determined but highest dose was 28.5 g/kg.</p> <p>Overall toxicity very low.</p>	<p>OS-57</p> <p>Handwritten note indicates study was with Pydraul 150.</p> <p>Not Pure Aroclor Organophosphate with 52.5% Aroclor 1248 added. I THINK THIS WAS COPIED. NOT SURE IT IS CORRECT.</p>
<p>18. 1955 (0200)</p> <p>TOXICOLOGICAL INVESTIGATION OF PYDRAUL F-9 (FH-103).</p> <p>Fred Younger, Scientific Associates</p>	<p>The oral LD50 (rat) was 24 g/kg.</p> <p>Skin absorption MLD (rabbit): 2.0-2.8 g/kg.</p> <p>Low dermal and eye irritation.</p> <p>why the lethal dose was greater with dermal absorption than oral administration.</p>	<p>Pydraul F-9: Organophosphate with 52.5% Aroclor 1248 added.</p> <p>Animals were exposed to Pydraul F-9 and acute toxicity evaluated with oral, eye and skin exposures.</p>
<p>19. 1955 (0206)</p> <p>Toxicological investigation of Fluid OS-63</p> <p>Fred Younger, Scientific Associates</p>	<p>The oral LD50 (rat) was 17 g/kg.</p> <p>Skin absorption MLD (rabbit) : 2.4-3.0 g/kg</p> <p>Low dermal and eye irritation.</p> <p>Why the lethal dose was greater with dermal absorption than oral administration.</p>	<p>Animals were exposed to Fluid OS-63 and acute toxicity evaluated with oral, eye and skin exposures.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>20. June 22, 1955 (0212)</p> <p>THE TOXICITY OF THE VAPOR OF AROCLORS 1242 AND 1254.</p> <p>Treon, Cleveland, Shaffer, Cappel, Atchley, Torbeck, Wagner. Kettering Laboratory, University of Cincinnati.</p>	<p>Study results are invalidated due to the wide spread epidemic of pneumonia infection and ill health of colony of laboratory animals.</p> <p>Should not be considered a “toxicity” study since the majority of the “health” endpoints were death and body weight.</p> <p>Concludes that mortality was due to natural pneumonia infections not Aroclors.</p> <p>Authors state that although mortality rate was not increased: “For practical purposes this conclusion is subject to the critique of further experiments involving more prolonged exposure of animals to somewhat lower concentrations.”</p>	<p>Aroclor 1242, 1254 inhalation study. Several endpoints measured but findings negated by poor health of animals.</p>
<p>21. June 28, 1955 (0314)</p> <p>THE TOXICITY OF THE VAPOR OF AROCLOR 1242 AND OF AROCLOR 1254.</p> <p>Treon, Cleveland, Shaffer, Cappel, Boller, Torbeck, Kettering Laboratory, University of Cincinnati.</p>	<p>Study was a supplement to earlier study. Results are largely invalid. There was wide spread epidemic of pneumonia infection and ill health of colony of laboratory animals. The mortality rate of all animals-including controls-was unacceptably high.</p> <p>States that there were no gross or microscopic evidence of pathology with Aroclor 1242 although</p> <p>Aroclor 1254 exposures produced lesions in livers and kidneys. Authors state that prolonged respiratory exposure to Aroclor 1254 is capable of causing some injury to the tissues of susceptible animals...</p>	<p>Not a study. Aroclor 1242, 1254</p>
<p>21. July 5 1955 (0388)</p> <p>THE TOXICITY OF A MIST GENERATED BY THE ASPIRATION OF PYDRAUL.</p> <p>Treon, Cleveland, Atchley. Kettering Laboratory, University of Cincinnati.</p>	<p>Specific purpose was to determine if Pydraul vapors produced during simulation of a catapult system on an aircraft carrier were toxic from an acute exposure.</p> <p>Following 2 or 4 hr. to 0.45 mg/L exposures guinea pigs died. Cats, rabbits, and rats survived; livers and kidneys were examined after sacrifice, and cats and rabbits exhibited degenerative changes.</p>	<p>Not pure Aroclor. Specific type of Pydraul; organophosphate/aroclor added not identified. Pydraul is not pure Aroclor.</p> <p>Endpoint was death.</p>
<p>22. 1955 (0404)</p> <p>TOXICOLOGICAL INVESTIGATION OF PYDRAUL 600.</p> <p>Fred Younger, Scientific Associates</p>	<p>Screening toxicity study for oral lethal dose and eye and skin irritation.</p> <p>Only gross observation of organs. No cause of death.</p> <p>Oral LD50 (rat) = 30.5 g/kg.</p> <p>Skin absorption MLD (rabbit) : 3.9–5.2 g/kg.</p> <p>Slight skin and eye irritation with Draize test. No deaths on vapor inhalation.</p>	<p>Pydraul 600. Not Pure Aroclor. Precise chemical composition not known, but Pydraul 625 is Organophosphate containing 50% Aroclor 1260.</p>
<p>23. 1955 (0410)</p> <p>TOXICOLOGICAL INVESTIGATION OF PYDRAUL 600.</p> <p>Fred Younger, Scientific Associates</p>	<p>Follow-up to previous study with single dose of 25.0 g/kg.</p> <p>Oral LD50 is ~0.72 g/kg for rabbits. The compound proved to be much more toxic for rabbits than for mice.</p>	<p>Pydraul 600. Not Pure Aroclor. Precise chemical composition not known, but Pydraul 625 is Organophosphate containing 50% Aroclor 1260.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>24. 1956 (0413)</p> <p>TOXICOLOGICAL INVESTIGATION OF PYDRAUL AC (OS-67)</p> <p>Fred Younger, Younger Laboratories</p>	<p>Screening Study for oral lethal dose, eye and skin irritation, and inhalation exposure</p> <p>Oral LD50 (rats) : 52 g/kg</p> <p>Oral MLD (rabbits) : 3.5–4.5 g/kg</p> <p>Skin Absorption MLD (rabbits) : 4.0–5.0 g/kg</p> <p>Slight skin and eye irritation with Draize test. Survived inhalation for 6 hours.</p>	<p>Pydraul AC: Not Pure Aroclor, 5-Ring Polyphenyl Ether organophosphate</p>
<p>25. 1957 (0420)</p> <p>TOXICOLOGICAL INVESTIGATION OF: HYDRAULIC FLUID OS-81- MONSANTO SAMPLE NO.1; HYDRAULIC FLUID OS-83 – MONSANTO SAMPLE NO.2</p> <p>Fred Younger, Younger Laboratories</p>	<p>Screening Study for oral lethal dose, eye and skin irritation, and inhalation exposure</p> <p>OS-81: Oral LD50 (rat) : 8.6 g/kg</p> <p>Oral MLD (rabbit) : 0.35–0.5 g/kg</p> <p>Mild skin, eye, inhalation</p> <p>OS-83: Oral LD50 (rat) : 34.3 g/kg</p> <p>Oral MLD (rabbit) : 4.25–5.0 g/kg</p> <p>Mild skin, eye, inhalation</p>	<p>Aromatic Ether-Not Pure Aroclor</p>
<p>26. 1957 (0430)</p> <p>TOXICOLOGICAL INVESTIGATION OF AROCLOR 1270 AMMONIA REACTION PRODUCT</p> <p>Fred Younger, Younger Laboratories</p> <p>3 Pages</p>	<p>Screening Study for oral lethal dose, eye and skin irritation exposure.</p> <p>Oral LD50 (rat) : 7.10 g/kg</p> <p>mild eye and skin irritation</p>	<p>Not Pure Aroclor. Aroclor 1270 Ammonia Reaction Product</p>
<p>27. 1958 (0433)</p> <p>TOXICOLOGICAL INVESTIGATION OF OS-95</p> <p>Fred Younger, Younger Laboratories</p>	<p>Screening Study for oral lethal dose, eye and skin irritation exposure.</p> <p>Oral LD50 (rat) : 10.5 g/kg,</p> <p>Skin absorption MLD (rabbit) : 0.63–1.25 g/kg</p> <p>mild eye and skin irritation, and mild inhalation</p>	<p>Not Pure Aroclor. 5 Ring Polyphenyl Ether Product</p>
<p>28. 1958 (0440)</p> <p>THE TOXICITY OF THE THERMAL DECOMPOSITION PRODUCTS OF ‘PYDRAUL 625’</p> <p>Fred Younger, Younger Laboratories</p>	<p>Rats were exposed to “fogs” of Pydraul that was superheated.</p> <p>Moderate mist 6hrs 2/8 deaths (18 and 21 days) .</p> <p>Heavy Mist 15 min. all rats survived.</p> <p>Heavy Mist 1hr. all survived</p>	<p>Pydraul 625. Not Pure Aroclor. Organophosphate containing 50% 1260. General observations of animals after exposures. Death was the endpoint</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>29. 1958 (0448)</p> <p>TOXICOLOGICAL INVESTIGATION OF THE FOLLOWING COMPOUNDS</p> <p>1.POLYCHLORINATED BISPHENOL (HYDROLYZED AROCLOR 1268) , SAMPLE NO. 119; 2) DIGLYCIDYL ETHER OF TETRACHLOROBISPHENOL A (?) , SAMPLE NO 120; 3) DIGLYCIDYL ETHER OF POLYCHLORINATED BISPHENOL, SAMPLE NO. 121</p> <p>REST OF TITLE AND TEXT MOSTLY ILLEGIBLE.</p>	<p>Single Dose Screening Study for oral and dermal lethal dose.</p> <p>1.POLYCHLORINATED BISPHENOL (HYDROLYZED AROCLOR 1268),</p> <p>Oral LD50 (rat): 785 mg/kg</p> <p>Skin absorption lethal dose (rabbit) : >2.5 g/kg and <3.25 g/kg</p> <p>2) DIGLYCIDYL ETHER OF TETRACHLOROBISPHENOL A (?)</p> <p>Oral LD50 (rat): 28.8 g/kg</p> <p>Skin absorption (rabbit) : highest application of 10 g/kg was nonlethal</p> <p>3) DIGLYCIDYL ETHER OF POLYCHLORINATED BISPHENOL</p> <p>Oral LD50 (rat): 5.5 g/kg</p> <p>Skin absorption (rabbit): highest application of 10 g/kg was nonlethal</p> <p>All, non to mild eye and skin irritants</p>	<p>Not Pure Aroclor. Hydrolyzed Aroclor 1268.</p>
<p>30. 1958 (0463)</p> <p>TOXICOLOGICAL INVESTIGATION OF OS-95.</p> <p>Fred Younger, Younger Laboratories</p>	<p>Screening study for skin absorption and irritation.</p> <p>Sample 102, Lot 7501-3677</p> <p>Skin absorption MLD (rabbit) : 2–2.5 g/kg</p> <p>Sample 17, Lot S-59</p> <p>Skin absorption MLD (rabbit) : 1.25–1.5 g/kg</p> <p>Both, mild to moderate skin irritants.</p>	<p>Not Pure Aroclor. 5-Ring Polyphenyl Ether</p>
<p>31. 1958 (0467)</p> <p>THE TOXICITY OF THE THERMAL DECOMPOSITION PRODUCTS OF ‘OS-95’</p> <p>Fred Younger, Younger Laboratories</p>	<p>Exposure to fog of thermal decomposition products.</p> <p>Moderate mist (6 h): no deaths</p> <p>Heavy conc (15 min): no deaths.</p> <p>Heavy conc (1 h): No deaths.</p>	<p>Not Pure Aroclor. 5-Ring Polyphenyl Ether</p>
<p>32. 1962 (0475)</p> <p>TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1232.</p> <p>Fred Younger, Younger Laboratories.</p>	<p>Oral LD50 (rat) : 4.47 g/kg</p> <p>Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg</p>	<p>Aroclor 1232. Single dose skin irritation and death.</p>
<p>33. 1962 (0479)</p> <p>TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1221.</p> <p>Fred Younger, Younger Laboratories.</p>	<p>Single dose oral LD50 study and dermal LD50 study.</p> <p>Oral LD50 (rat) : 4.98 g/kg (slightly toxic)</p> <p>Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly)</p>	<p>Aroclor 1221. Single dose death skin irritation and death.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
34. 1962 (0483) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1242. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 8.65 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >794 g/kg and < 1.26 g/kg (moderately toxic)	Aroclor 1242. Single dose death skin irritation and death.
35. 1962 (0487) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1248 Fred Younger, Younger Laboratories	Oral LD50 (rat) : 12.5 g/kg (practically nontoxic) Skin absorption MLD (rabbit) : >794 g/kg and <1.26 g/kg	Aroclor 1248
36. 1962 (0491) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1260. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 10 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg (moderately toxic)	Aroclor 1260. Single dose skin irritation and death.
37. 1962 (0495) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1254. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 11.9 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg (moderately toxic)	Aroclor 1254. Single dose skin irritation and death.
38. 1962 (0499) TOXICOLOGICAL INVESTIGATION OF AROCLOR: 1262. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 11.3 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <3.16 g/kg (mildly toxic)	Aroclor 1262. Single dose skin irritation and death.
39. 1962 (0503) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 4465. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 16 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : > 2 g/kg and <3.16 g/kg (slightly toxic) Mild skin irritation, moderate eye irritant.	Not Pure Biphenyl Aroclor. Aroclor 4465: Terphenyl Single dose skin irritation and death.
40. 1962 (0509) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1268. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 10.9 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : highest application = 2.51 g/kg (slightly toxic) Mild skin irritation, moderate eye irritant.	Aroclor 1268. Aroclor Single dose skin irritation and death.
41. 1962 (0513) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 2565. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 6.31 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly toxic) Mild skin irritation.	Not Pure Bi-phenyl Aroclor. Aroclor 2565: 25% Terphenyl and 75% Aroclor 1265. Single dose skin irritation and death.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>42. 1963 (0517)</p> <p>TOXICOLOGICAL INVESTIGATION OF: PYRANOL 1470.</p> <p>Fred Younger, Younger Laboratories.</p>	<p>Single dose oral LD50 study and dermal MLD50 study.</p> <p>Oral LD50 (rat) : 2.25 g/kg (slightly toxic)</p> <p>Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly toxic)</p> <p>Moderate skin irritation, moderate eye irritant, slightly toxic with inhalation.</p>	<p>Pyranol 1470. Aroclor 1254 Electrical Grade.</p> <p>Single dose oral and dermal death and irritation.</p>
<p>43. 1963 (0525)</p> <p>TOXICOLOGICAL INVESTIGATION OF: INERTEEN PPO.</p> <p>Fred Younger, Younger Laboratories.</p>	<p>Single dose oral LD50 study and dermal MLD50 study.</p> <p>Oral LD50 (rat) : 2.37 g/kg (slightly toxic)</p> <p>Skin absorption MLD (rabbit) : >3.16 g/kg and <5.01 g/kg (slightly toxic)</p> <p>Moderate skin irritation, moderate eye irritant, slightly toxic with inhalation.</p>	<p>Inerteen PPO. Not pure Aroclor-Dilute product of PCBs and mineral oil. Acute death and irritation body surfaces.</p>
<p>44. 1963 (0533)</p> <p>SUBACUTE DERMAL TOXICITY OF AROCLOR 1248.</p> <p>Richard Palazzolo, Industrial Bio-Test Laboratories, Inc.</p>	<p>Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 10,50, 100 mg/kg/day. End point was primarily skin irritation.</p> <p>50% of 50 mg/kg/day and all 100 mg/kg/day died.</p> <p>LD 50 = 50 mg/kg/day</p> <p>LD 0.01 = 16.8 mg/kg/d</p> <p>LD 99.99 = 150 mg/kg/d</p> <p>Liver discoloration in 50 and 100 groups with moderate necrosis in 50. Animals that died were not examined.</p>	<p>Aroclor 1248. Primary interest was LD50 and skin irritation with subacute 20 day exposures</p>
<p>45. 1963 (0549)</p> <p>SUBACUTE DERMAL TOXICITY OF AROCLOR 1242.</p> <p>Richard Palazzolo, Industrial Bio-Test Laboratories, Inc.</p>	<p>Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 50, 75, 100 mg/kg/day. End point was primarily skin irritation.</p> <p>50% of 50 mg/kg/day and all 100 mg/kg/day died.</p> <p>LD 50 = 75 mg/kg/day</p> <p>LD 0.01 = 44 mg/kg/d</p> <p>LD 99.99 = 128 mg/kg/d</p> <p>Liver discoloration in 50 and 100 groups with moderate necrosis in 50. Animals that died were not examined.</p>	<p>Aroclor 1242. Primary interest was LD50 skin irritation with subacute 20 day exposures</p>
<p>46. 1963 (0566)</p> <p>SUBACUTE DERMAL TOXICITY OF AROCLOR 1268.</p> <p>Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.</p>	<p>Subacute dermal exposure. Four test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 500, 1000, 1500, and 2000 mg/kg/day. End point was primarily skin irritation.</p> <p>All animals in 1500 and 2000 mg/kg/day groups died.</p> <p>LD 50 = 1250 mg/kg/d</p> <p>LD 0.01 = 635 mg/kg/d</p> <p>LD 99.99 = 2450 mg/kg/d</p>	<p>Aroclor 1268. Primary interest was LD50 skin irritation with subacute 20 day exposures</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
	Moderate hepatic necrosis in Liver in two high dose groups. Animals that died were not examined.	
<p>47. 1963 (0602)</p> <p>SUBACUTE DERMAL TOXICITY OF AROCLOR 1254.</p> <p>Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.</p>	<p>Subacute dermal exposure. Four test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 10, 50, 100, 200 mg/kg/day. End point was primarily skin irritation.</p> <p>50% of animals in 50 and 100 groups died; 100% of animals in 200 group died</p> <p>LD 50 = 75 mg/kg/day</p> <p>LD 0.01 = 6.2 mg/kg/d</p> <p>LD 99.99 = 915 mg/kg/d</p> <p>Moderate liver necrosis seen in 50 and 100 group. Animals that died were not examined.</p>	<p>Aroclor 1254. Primary interest was LD50 and skin irritation with subacute 20 day exposures</p>
<p>48. 1963 (0620)</p> <p>SUBACUTE DERMAL TOXICITY OF AROCLOR 4465.</p> <p>Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.</p>	<p>Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 75, 150, 300 mg/kg/day. End point was primarily skin irritation.</p> <p>50% of animals at 150, 100% died at 300</p> <p>LD 50 = 150 mg/kg/day</p> <p>LD 0.01 = 76 mg/kg/d</p> <p>LD 99.99 = 300 mg/kg/d</p> <p>Hepatic cell necrosis and vacuolization with mononuclear white blood cell infiltration in 150 group.</p> <p>Animals that died were not examined.</p>	<p>Aroclor 4465 – Not a pure Aroclor biphenyl. 40% terphenyl and 65% Aroclor with 65% chlorine. Primary interest was dermal LD50 and skin irritation with subacute 20 day exposures</p>
<p>49. 1963 (0637)</p> <p>TOXICOLOGICAL INVESTIGATION OF: MCS-300.</p> <p>Fred Younger, Younger Laboratories.</p>	<p>Acute exposure study</p> <p>Rat oral LD50: 8.9 g/kg</p> <p>Rabbit skin absorption MLD: >3.98 g/kg and < 6.31 g/kg</p> <p>Rabbit Skin irritation - moderate</p> <p>Rabbit Eye irritation - mild</p> <p>Rat Vapor inhalation - nontoxic</p>	<p>MCS – 300. Not an Aroclor. Aromatic Ether.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
50. 1964 (0645) TOXICOLOGICAL INVESTIGATION OF: FH-145. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.68 g/kg Oral MLD (rabbit) : >1 g/kg and <1.58 g/kg Skin absorption MLD (rabbit) : >2.51 g/kg and <3.98 g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation - mild Rat Vapor inhalation – slightly toxic.	FH 145-330 (?) – Does not appear to be an Aroclor.
51. 1964 (0654) TOXICOLOGICAL INVESTIGATION OF: MCS-295. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.2 g/kg Skin absorption MLD (rabbit) : >0.5 g/kg and <0.8 g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation – moderate Rat Vapor inhalation – nontoxic.	MCS-295. Not a pure Aroclor. Aromatic Ether
52. 1964 (0662) TOXICOLOGICAL INVESTIGATION OF: FH 159. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.9 g/kg Skin absorption MLD (rabbit) : >1.5 g/kg and <2.61 (?) g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation – moderate Rat Vapor inhalation – nontoxic.	FH-159 - Not a Pure Aroclor.
53. 1964 (0670) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 280. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 11.8 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation - moderate toxic Rabbit Eye irritation – moderate toxic Rat Vapor inhalation – mildly toxic	Pydraul 280. Not a Pure Aroclor. Organophosphate with PCB added.
54. 1964 (0678) TOXICOLOGICAL INVESTIGATION OF: MCS 312. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.5 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Rabbit Skin irritation – slight skin irritant Rabbit Eye irritation – slight eye irritant Rat Vapor inhalation – practically nontoxic	MCS 312. Not an Aroclor. Aromatic Ether

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
55. 1966 (0686) TOXICOLOGICAL INVESTIGATION OF: MCS 395. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.6 g/kg Oral MLD (rabbit) : 1.6 g/kg Skin absorption MLD (rabbit) : >2.5 g/kg and <4.0 g/kg Rabbit Skin irritation – nonirritating Rabbit Eye irritation – slight irritant Rat Vapor inhalation – non-toxic	MCS 395. Not an Aroclor. Aromatic Ether
56. 1966 (0695) TOXICOLOGICAL INVESTIGATION OF: MCS-404. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 19.8 g/kg Oral MLD (rabbit) : 1.6 g/kg/day Skin absorption MLD (rabbit) : > 1.0 g/kg and <1.6 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – slight toxic Rat Vapor inhalation – non-toxic	MCS-404. Not a pure Aroclor. Aromatic Ether
57. 1966 (0704) TOXICOLOGICAL INVESTIGATION OF: MCS 90. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 3.3 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.2 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – moderate toxic Rat Vapor inhalation – non-toxic	MCS 90. Not a pure Aroclor. Aromatic Ether
58. 1966 (0712) TOXICOLOGICAL INVESTIGATION OF: MCS 528. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.4 g/kg Skin absorption MLD (rabbit) : > 0.79 g/kg and <1.26 g/kg	MCS 528. Not a pure Aroclor. Aromatic Ether
59. 1966 (0716) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL AC. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 18.9 g/kg Skin absorption MLD (rabbit) : > 0.79 g/kg and <1.26 g/kg	PYDRAUL AC. Not a pure Aroclor. Organophosphate 47% containing 57% Aroclor 1254.
60. 1966 (0720) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 280. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.4 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Liver dehydration and discoloration.	PYDRAUL 280. Not a pure Aroclor. Organophosphate containing PCBs.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
61. 1966 (0724) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 135. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.2 g/kg g/kg/day Skin absorption MLD (rabbit) > 1.26 g/kg and <2.0 g/kg Liver dehydration and discoloration.	PYDRAUL 135. Not a pure Aroclor. Organophosphate containing 9.5% Aroclor 1232, 36.5% Aroclor 1242
62. 1966 (0728) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 625. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 20.7 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Liver discoloration.	PYDRAUL 625. Not a pure Aroclor. Organophosphate containing 50% Aroclor 1260
63. 1966 (0732) TOXICOLOGICAL INVESTIGATION OF: MCS 404. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 15.0 g/kg Skin absorption MLD (rabbit) : > 1.26 g/kg and <2.0 g/kg	MCS 404. Chemical Composition Unknown.
64. 1966 (0736) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL F-9. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 11.2 g/kg Skin absorption MLD (rabbit) : > 0.5 g/kg and <0.8 g/kg	Pydraul F-9. Not a pure Aroclor. Organophosphate containing 52.5% Aroclor 1248
65. 1966 (0740) TOXICOLOGICAL INVESTIGATION OF: MCS 153. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 7.9 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg	MCS-153. Chemical composition unknown.
66. 1967 (0744) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 230. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 10.5 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – mild irritant Rat Vapor inhalation – non-toxic	PYDRAUL 230. Organophosphate containing 3.0 % Aroclor 1221, 54.7 Aroclor 1242
67. 1967 (0752) TOXICOLOGICAL INVESTIGATION OF: (XA-140) SANTICIZER 1706. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.9 g/kg	SANTICIZER 1706 Chemical composition unknown

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
68. 1969 (0754) TOXICOLOGICAL INVESTIGATION OF: SANTOSAFE 300 (MCS-528) OR-116021. Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.9 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant	Santosafe 300. Chemical composition unknown
69. 1969 (0760) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 312 (MCS-312) OR-116021 Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 5.3 g/kg Skin absorption MLD (rabbit) : > 3.2 g/kg and <5.0 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant	Pydraul 312. Organophosphate containing 47.3% Aroclor 1242.
70. 1969 (0766) 30-DAY TISSUE COLLECTION STUDY IN ALBINO RATS WITH AROCLORS BTL-AROCOLOR II James Plank, Industrial Bio-Test Laboratories, Inc. Tissues Sent To: Dr. Hunt, Monsanto	Not A Toxicology Study IBT – Conducted the feeding. Animals were sacrificed and tissues were shipped to Monsanto. Monsanto conducted	Aroclor II. 1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - <u>Terphenyls</u> 4. Aroclor 5460 5. Halowax 1014 62% Cl 6. Halowax 1099 52% Cl Non Aroclors 7. Toxaphene 8. DDT
71. 1969 (0773) CHICKEN RESIDUE STUDIES ON AROCLORS AND VARIOUS OTHER MATERIALS BTL-AROCOLOR Allen Wolvin, Industrial Bio-Test Laboratories, Inc. Tissues Sent To: Dr. Hunt, Monsanto	Two Phase 1. Determine LD50 2. 7-day feeding at 1/5 LD50 dose Results: Oral LD50 for 4 Aroclors, 2 Halowax materials, and DDT: > 10 g/kg TOXAPHENE oral LD50: 0.316 g/kg No Toxicity Data Presented	1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - <u>Terphenyls</u> 4. Aroclor 5460 5. Halowax 1014 62% Cl 6. Halowax 1099 52% Cl Non Aroclors 7. Toxaphene 8. DDT

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
72. 1969 (0789) TOXICOLOGICAL INVESTIGATION OF: MCS 900 Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 1.3 g/kg/day Skin absorption MLD (rabbit) : > 7.9 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant Vapor inhalation Non-toxic	MCS 900 Chemical composition unknown.
73. 1969 (0798) FOUR-DAY FISH TOXICITY STUDIES ON SEVEN MATERIALS Carmen Mastri, Industrial Bio-Test Laboratories, Inc. Sent to: Mr. Wheeler, Hunt, Monsanto	Acute 4-Day exposure to Trout and Blue Gill to determine LC50 Trout LC50 (4-day, ppm) 1. Aroclor 1242: >100 ppm 2. Aroclor 1254: >100 ppm 3. Aroclor 1260: >100 ppm 4. Aroclor 5460: >100 ppm 5. Toxaphene: 0.008 ppm 6. DDT 0.0052 7. Halowax 1099: (10–100 ppm) Blue Gill LC50 (4-day, ppm) 1. Aroclor 1242: 0.66 ppm 2. Aroclor 1254: 0.66 ppm 3. Aroclor 1260: >100 ppm 4. Aroclor 5460: >100 ppm 5. Toxaphene: 0.0056 ppm 6. DDT: 0.0078 ppm 7. Halowax 1099: (>100 ppm) Parentheses indicate range-finding data	1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - <u>Terphenyls</u> 4. Aroclor 5460 5. Halowax 1099 52% Cl Non Aroclors 6. Toxaphene 7. DDT
74. 1969 (0832) TOXICOLOGICAL INVESTIGATION OF: MCS 9001 Melvin Birch, Younger Laboratories, Inc.	Acute exposure study causing death. Oral LD50 (rat) : 1.2 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <2.0 g/kg Rabbit Skin irritation – non irritating Rabbit Eye irritation – slight irritant Vapor inhalation slightly toxic	MCS 9001 Chemical composition unknown.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>75. 1970 (0840)</p> <p>TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 281—Lot QL-42</p> <p>Melvin Birch, Younger Laboratories, Inc.</p>	<p>Acute exposure study causing death.</p> <p>Oral LD50 (rat) : 10.4 g/kg</p> <p>Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg</p> <p>Rabbit Skin irritation – mild to moderate irritant</p> <p>Rabbit Eye irritation – mild irritant</p> <p>Vapor inhalation</p> <p>non toxic</p>	<p>PYDRAUL 281 Organophosphate containing unknown PCB composition.</p>
<p>76. 1970 (0848)</p> <p>TOXICOLOGICAL INVESTIGATION OF: MCS 1009</p> <p>Melvin Birch, Younger Laboratories, Inc.</p>	<p>Acute exposure study causing death.</p> <p>Oral LD50 (rat) : 7.7 g/kg</p> <p>Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg</p> <p>Rabbit Skin irritation – moderate irritating</p> <p>Rabbit Eye irritation – slight irritant</p> <p>Vapor inhalation</p> <p>non toxic</p>	<p>MCS 1009.</p> <p>Unknown composition.</p>
<p>77. 1970 (0856)</p> <p>TOXICOLOGICAL INVESTIGATION OF: MCS 999</p> <p>Melvin Birch, Younger Laboratories, Inc.</p>	<p>Acute exposure study causing death.</p> <p>Oral LD50 (rat) : 11.8 g/kg</p> <p>Skin absorption MLD (rabbit) : >3.2 g/kg and <5.0 g/kg</p> <p>Rabbit Skin irritation –mild irritating</p> <p>Rabbit Eye irritation – slight irritant</p> <p>Vapor inhalation</p> <p>non toxic</p>	<p>MCS 999.</p> <p>Unknown composition.</p>
<p>78. 1970 (0864)</p> <p>TOXICITY, REPRODUCTION AND RESIDUE STUDY ON AROCLOR 1242, LOT #AK-255; AROCLOR 1254, LOT #AK-38; AROCLOR 1260, LOT #AK-3 IN WHITE LEGHORN CHICKENS</p> <p>James Stephens,</p> <p>Industrial Bio-Test Laboratories, Inc.</p>		<p>1. Aroclor 1242</p> <p>2. Aroclor 1254</p> <p>3. Aroclor 1260</p>
<p>79. 1970 (0950)</p> <p>TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6062—LOT QM 1304</p> <p>Melvin Birch, Younger Laboratories, Inc.</p>	<p>Acute single dose exposure study causing death.</p> <p>Oral LD50 (rat) : 8.1 g/kg</p> <p>Skin absorption MLD (rabbit) : > 7.9 g/kg</p> <p>Rabbit Skin irritation –slight irritating</p> <p>Rabbit Eye irritation – slight irritant</p>	<p>Aroclor 6062. Not Pure Biphenyl Aroclor.</p> <p>Aroclor 6062-Blend of Aroclor 5460 (which is a Terphenyl) and Aroclor 1221</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
80. 1970 (0957) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6037—MCS 1057-1 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 4.9 g/kg g/kg/day Skin absorption MLD (rabbit) : >5.0 g/kg and <7.9 g/kg Rabbit Skin irritation –mild irritating Rabbit Eye irritation – slight irritant inhalation: non-toxic	Aroclor 6037
81. 1970 (0965) TOXICOLOGICAL INVESTIGATION OF: MCS 1004--AROCLOR 4273, LOT NUMBER: OR 151723-3 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 8.9 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.2 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 4273. Not Pure Biphenyl Aroclor. Aroclor 4273-40% Terphenyl and 60% Aroclor 73% chlorine
82. 1970 (0974) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6040—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 3.3 g/kg Skin absorption MLD (rabbit) : > 3.2 g/kg and <5.0 g/kg Rabbit Skin irritation –moderate to severe irritation Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 6040. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
83. 1970 (0982) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6070—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 4.0 g/kg Skin absorption MLD (rabbit) : >7.9 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 6070. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
84. 1970 (0990) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6090—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Range finding acute oral toxicity (rat) : >10 g/kg and <12.6 g/kg Skin absorption MLD (rabbit) : >7.9 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant	Aroclor 6090. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
85. No Date-1970?? (0996) TOXICOLOGICAL STUDIES WITH POLYCHLORINATED BIPHENYLS. M.L. Keplinger et al. Industrial Bio-Test Laboratories, Inc.	Study prompted by reports of PCBs detected in wildlife. Key findings was evidence of reproductive toxicity and tumor formation. 1. This is the first Monsanto study that investigates the toxicological effects of CHRONIC exposures.	Aroclors 1242, 1254, and 1260. No raw data presented to evaluate. Preliminary 30-day rat study conducted to determine the “no apparent effect” of 1254 and 1260.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
	<p>Notes that up until this time (1970?) no information on chronic exposures was available. It is also the first study where ingestion from the diet was evaluated.</p> <p>“Although some toxicological data were available, they were rather limited. Information on chronic effects especially of the PCB’s were not available.”</p> <p>2. First noted appearance of tumors in chickens.</p>	<p>2-year rat study used 1, 10 and 100 ppm. 2-year dog feeding study.</p> <p>100 ppm 1254 and 1260 caused increased liver weight.</p> <p>Three generation study: First generation showed 1254 had reproductive toxicity-lactation index decrease. Mating indices were reduced.</p> <p>Second generation showed decreased survival with 1242 and lactation decrease with 1254.</p> <p>Chicken fed diet with 1242 and 1254 lower body weight. Chickens also showed “<u>extensive growths</u>” on the kidneys, gonads, liver or heart.</p>
<p>86. 1971 (1002)</p> <p>REPORT TO MONSANTO COMPANY ACUTE VAPOR INHALATION TOXICITY STUDY WITH MCS 1016 IN ALBINO RATS</p> <p>Donn Hathaway, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Acute inhalation study with 10 rats to a 4-hour period-14-day observation.</p> <p>Endpoint was death from acute exposures. No deaths.</p>	<p>MCS 1016. Aroclor 1016 is a refined Aroclor 1242 developed after 1971.</p>
<p>87. 1971 (1008)</p> <p>REPORT TO MONSANTO COMPANY ACUTE TOXICITY STUDIES WITH AROCLOR 1221, AROCLOR 5442, AND MCS 1016</p> <p>Carmen Mastri, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Acute study with one dose.</p> <p>Aroclor 1221:</p> <p>Acute oral toxicity, LD50 (rat) : 2.0 g/kg.</p> <p>Acute dermal toxicity, LD50 (rabbit) : 5.0 g/kg</p> <p>Eye irritation-rabbits- minimally irritating.</p> <p>Skin irritation-rabbits- moderately irritating.</p> <p>Aroclor 5442:</p> <p>Acute oral toxicity, LD50 (rat) : 8.4 g/kg.</p> <p>Acute dermal toxicity, LD50 (rabbit) : >10.2 g/kg</p> <p>Eye irritation-rabbits- non-irritating.</p> <p>Skin irritation-rabbits- moderately irritating</p> <p>MCS 1016:</p> <p>Acute oral toxicity, LD50 (rat) : 6.8 g/kg.</p> <p>Acute dermal toxicity, LD50 (rabbit) : 6.0 g/kg</p> <p>Eye irritation-rabbits- non irritating.</p> <p>Skin irritation-rabbits- moderately irritating</p>	<p>Aroclor 1221, 5442, and MCS 1016.</p> <p>Aroclor 5442 is not a pure biphenyl. It is a terphenyl and biphenyl mixture. MCS 1016 is a refined Aroclor 1242 developed after 1971.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>88. 1971 (1049)</p> <p>REPORT TO MONSANTO COMPANY TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH AROCLOR 1242, LOT #AK-255 IN WHITE LEGHORN CHICKENS</p> <p>Dale Flecher, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Subchronic chicken feeding study.</p> <p>Aroclor 2, 4, and 8 ppm mixed in diet for 39 weeks (ave. chicken life span 15 years)</p> <p>No specific effects noted.</p> <p>Tissues were collected and shipped to Monsanto, and Monsanto findings were not reported in this study.</p>	<p>Aroclor 1242.</p> <p>Effect of Aroclor on egg laying.</p>
<p>89. 1971 (1085)</p> <p>TOXICOLOGICAL INVESTIGATION OF: DECACHLOROBIPHENYL-AROCLOR 1272—LOT: OR 179021</p> <p>Melvin Birch, Younger Laboratories, Inc.</p>	<p>Acute single dose exposure study causing death.</p> <p>Acute Oral MLD (rat) : >7.9 g/kg</p> <p>Skin absorption MLD (rabbit) : >7.9 g/kg</p> <p>Rabbit Skin irritation –non-irritating</p> <p>Rabbit Eye irritation – slight irritant</p>	<p>Aroclor 1272.</p> <p>Blend of Terphenyl and Aroclor.</p>
<p>90. 1971 (1091)</p> <p>REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1254 IN ALBINO RATS</p> <p>James Plank, Industrial BIO-TEST Laboratories, Inc.</p>	<p>First study to evaluate the teratologic effects of Aroclors on rats.</p> <p>Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1242 killed on day 20.</p> <p>Maternal body weight reduction.</p> <p>Percent of females with resorption sites was elevated.</p> <p>Only gross teratogenic observations were made.</p> <p>12% of fetuses from females administered 30 mg/kg had caudal renal ectopia (abnormal positioning/development of kidney</p>	<p>Aroclor 1254.</p> <p>Fetal death and physical malformations in live fetuses evaluated.</p>
<p>91. 1971 (1111)</p> <p>REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1242 IN ALBINO RATS</p> <p>James Plank, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Evaluation of the teratologic effects of Aroclors on rats.</p> <p>Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1242 killed on day 20.</p> <p>Percent of females with resorption sites was elevated.</p>	<p>Aroclor 1242.</p> <p>Effect of Aroclor on egg laying.</p>
<p>92. 1971 (1129)</p> <p>REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1260 IN ALBINO RATS</p> <p>James Plank, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Evaluation of the teratologic effects of Aroclors on rats.</p> <p>Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1260 killed on day 20.</p> <p>Decrease in pregnant female body weight in both dose groups.</p> <p>Percent of females with resorption sites was elevated.</p>	<p>Aroclor 1260.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>93. 1971 (1147)</p> <p>REPORT TO MONSANTO COMPANY THREE-GENERATION REPRODUCTION STUDY WITH AROCLOR 1242 IN ALBINO RATS</p> <p>Sandra Haley, Industrial BIO-TEST Laboratories, Inc.</p>	<p>Evaluation of the 2nd litter obtained from the 3rd parental generation- reproductive toxicity in rats.</p> <p>Rats were dosed at 1, 10 and 100 ppm</p> <p>The F1 rats had increased brain and liver weights in 100 ppm group.</p> <p>100 ppm F2 rats had lower mating indices and reduced pregnancies. It was so low, the study was stopped at the F2 stage.</p>	<p>Aroclor 1242.</p>
<p>94. 1971 (1198)</p> <p>REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN BEAGLE DOGS</p> <p>Bruce Burtner, Industrial BIO-TEST Laboratories, Inc.</p> <p>Paul Wright and M.L.</p>	<p>It states it is a “chronic 2-year toxicity study.” It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs.</p> <p>Dogs were fed PCBs in diet at 1, 10 and 100 ppm.</p> <p>This study found no systemic toxicity or cancer.</p> <p>These findings do not appear to be credible.</p>	<p>Aroclor 1254.</p>
<p>95. 1971 (1276)</p> <p>REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1242 IN BEAGLE DOGS</p> <p>Bruce Burtner, Industrial BIO-TEST Laboratories, Inc.</p> <p>Paul Wright and M.L. Keplinger</p>	<p>It states it is a “chronic 2-year toxicity study.” It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs.</p> <p>Toxicological Parameters Evaluated in 1, 10 and 100 ppm-dosed dogs:</p> <p>Body weight</p> <p>Food Consumption</p> <p>Behavioral Reactions</p> <p>Hematologic Studies</p> <p>Blood Chemistry Studies</p> <p>Urine Analysis</p> <p>This study found no systemic toxicity or cancer.</p> <p>These findings do not appear to be credible.</p>	<p>Aroclor 1242.</p>
<p>96. 1971 (1351)</p> <p>REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN BEAGLE DOGS</p> <p>Bruce Burtner, Industrial BIO-TEST Laboratories, Inc.</p> <p>Paul Wright and M.L. Keplinger</p>	<p>It states it is a “chronic 2-year toxicity study.” It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs.</p> <p>Toxicological Parameters Evaluated in 1, 10 and 100 ppm-dosed dogs:</p> <p>Body weight</p> <p>Food Consumption</p> <p>Behavioral Reactions</p> <p>Hematologic Studies</p> <p>Blood Chemistry Studies</p> <p>Urine Analysis</p> <p>This study found no systemic toxicity or cancer.</p> <p>These findings do not appear to be credible.</p>	<p>Aroclor 1260.</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>97. 1971 (1426)</p> <p>REPORT TO MONSANTO COMPANY THREE-GENERATION STUDY WITH AROCLOR 1254 IN ALBINO RATS</p> <p>Sandra Haley, Industrial BIO-TEST Laboratories, Inc.</p> <p>James Plank, Paul Wright and M.L. Keplinger</p>	<p>Reproduction study to ascertain potential toxicological effects of subacute oral administration of Aroclor 1254. This report presents data from initiation of the investigation to weaning of the 2nd litters obtained from the 3rd parental generation.</p> <p>Rats fed 1, 10, or 100 ppm Aroclor 1254.</p> <p>Results. Body weight, mortality, reactions, gross pathologic findings, population data: no difference between control and test animals; liver weights and liver to body weight or brain weight ratios were significantly elevated in 100 ppm males; 2nd generation 100 ppm rats had lowered mating indices and reduced incidence of pregnancy; pup survival lower in litters from 100 ppm dams.</p>	<p>Aroclor 1254.</p>
<p>98. 1971 (1477)</p> <p>REPORT TO MONSANTO COMPANY THREE-GENERATION STUDY WITH AROCLOR 1260 IN ALBINO RATS.</p> <p>Sandra Haley, Industrial BIO-TEST Laboratories, Inc.</p> <p>James Plank, Paul Wright and M.L. Keplinger</p>	<p>Reproduction study, subacute oral administration of Aroclor 1260 in 3 generations of rats. Initiation to weaning of 2nd litters from 3rd parental generation.</p> <p>Rats fed 1, 10, or 100 ppm.</p> <p>Results. Body weight, mortality and reactions, gross pathology, lesions, population data, survival, body weights of progeny, pathology of progeny: no differences. Absolute liver weights and liver to body weight or brain weight ratios elevated in F0 and F1 males fed 100 ppm.</p>	<p>Aroclor 1260.</p>
<p>99. 1971 (1525)</p> <p>MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS.</p> <p>Philip Smith, Industrial BIO-TEST Laboratories, Inc.</p> <p>James Plank, Paul Wright and M.L. Keplinger</p>	<p>Chronic oral toxicity study. Rats fed 1, 10, or 100 ppm.</p> <p>Results. Food consumption, body weight gains, mortality, hematological and clinical blood chemistry, urine analyses, organ weights: no change. Liver weights and liver to body weight or brain weight ratios significantly elevated in 100 ppm rats, along with vacuolar changes; focal hypertrophy and focal hyperplasia found in livers of rats fed Aroclor 1260.</p>	<p>Aroclor 1260</p>
<p>100. 1971 (1612)</p> <p>MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY WITH AROCLOR 1254 IN ALBINO RATS.</p> <p>Philip Smith, Industrial BIO-TEST Laboratories, Inc.</p> <p>James Plank, Paul Wright and M.L. Keplinger</p>	<p>2-year chronic toxicity study. Rats fed 1, 10, or 100 ppm Aroclor 1254.</p> <p>Results. Body weight of females at 3 and 12 months, body weight of males at all time points, mortality, hematological and clinical blood chemistry, urine analyses, organ weights except liver: no change.</p> <p>Body weight at 24 mo. was less in 100 ppm females. Absolute liver weight and liver to body weight or brain weight ratios were significantly elevated in 100 ppm rats, with histologic exam revealing vacuolar changes. Focal hypertrophy and focal hyperplasia in livers of animals fed Aroclor 1254.</p>	<p>Aroclor 1254</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
<p>101. 1971 (1702)</p> <p>MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY WITH AROCLOR 1242 IN ALBINO RATS.</p> <p>Philip Smith, Industrial BIO-TEST Laboratories, Inc.</p> <p>James Plank, Paul Wright and M.L. Keplinger</p>	<p>2-year chronic oral toxicity study. Rats fed 1, 10, or 100 ppm Aroclor 1242.</p> <p>Results. Food consumption, body weight gains, mortality, hematological and clinical blood chemistry studies, urine analyses: no change. Liver weights and liver to body weight or brain weight ratios were significantly elevated in 100 ppm females. 100 ppm livers: vacuolar changes. Focal hypertrophy and focal hyperplasia in livers of rats fed Aroclor 1242.</p>	<p>Aroclor 1242</p>
<p>102. 1971 (1790)</p> <p>ACUTE TOXICITY OF AROCLOR 1016, AROCLOR 1242, AND DDT TO BLUEGIL (LEPOMIS MACROCHIRUS) AND CHANNEL CATFISH (ICTALURUS PUNCTATUS) DURING 21 DAYS CONTINUOUS EXPOSURE TO THE CHEMICALS IN WATER.</p> <p>Bevier Hasbrouck Sleight III, Bionomics, Inc.</p>	<p>Bioassay report. Median tolerance limit (TL50) developed.</p> <p>Results: Test fish behaved similar to chemically poisoned fish at Aroclor concentrations as low as 40 ug/l.</p> <p>Aroclor 1016, bluegill: 7-day TL50=>500.0 ug/l; 14-day TL50=186 ug/l; 21-day TL50=136 ug/l.</p> <p>Aroclor 1016, channel catfish: 7-d TL50=>500.0 ug/l; 14-d TL50=298 ug/l; 21-d TL50=138 ug/l.</p> <p>Aroclor 1242, bluegill: 7-d TL50=339 ug/l; 14-d TL50=163 ug/l; 21-d TL50=71.9 ug/l.</p> <p>Aroclor 1242, channel catfish: 7-d TL50=500.0 ug/l; 14-d TL50=391 ug/l; 21-d TL50=289 ug/l.</p> <p>DDT, bluegill: 7-d TL50=1.39 ug/l; 14-d TL50=0.887 ug/l; 21-d TL50=0.823 ug/l.</p> <p>DDT, channel catfish: 7-d TL50=>5.0 ug/l; 14-d TL50=3.83 ug/l; 21-d TL50=2.61 ug/l.</p>	<p>Aroclor 1016, Aroclor 1242, and DDT.</p> <p>Toxicity analyzed in bluegill and channel catfish over 21 days of continuous exposure to the chemicals in the water.</p>
<p>103. 1971 (1799)</p> <p>REPORT TO MONSANTO COMPANY. NINETY-DAY SUBACUTE ORAL TOXICITY STUDY WITH AROCLOR 1221 IN BEAGLE DOGS.</p> <p>Bruce Burtner, Industrial BIO-TEST Laboratories, Inc.</p> <p>Paul Wright and M.L. Keplinger</p>	<p>90-day subacute oral toxicity study. Dogs fed 1, 10, and 100 ppm for first 28 days. After 28 days, lowest level was increased from 1 ppm to 300 ppm; other levels remained the same.</p> <p>Results. No significant abnormalities</p>	<p>Aroclor 1221.</p> <p>Body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, histopathologic studies.</p>
<p>104. 1971 (1854)</p> <p>Manuscript for Toxicol. Appl. Pharmacol.</p> <p>TOXICOLOGICAL STUDIES OF THREE POLYCHLORINATED BIPHENYLS.</p> <p>O. Fancher, M.L. Keplinger, E.P. Wheeler, and J.C. Clandra.</p> <p>M.L. Keplinger co-author</p>	<p>Background review</p>	<p>Aroclor 1242, Aroclor 1254, Aroclor 1260</p>
<p>105. No date (1869)</p> <p>RESULTS OF FOUR-DAY STATIC FISH TOXICITY STUDIES RAINBOW TROUT.</p> <p>Industrial BIO-TEST Laboratories, Inc.</p>	<p>1.0% and 10.0% (w/v) soln in acetone.</p> <p>4-day TL50: >1.0 ppm</p>	<p>Aroclor 1260</p>

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
106. No date (1871) RESULTS OF FOUR-DAY STATIC FISH TOXICITY STUDIES RAINBOW TROUT AND BLUEGILLS. Gary Rausina, Industrial BIO-TEST Laboratories, Inc.	1.0% and 10.0% (w/v) solution in acetone 4-day TL50 (rainbow trout) : >10 ppm and <100.0 ppm; 4-day TL50 (bluegill) : >10 ppm and <100.0 ppm	Aroclor 1242
107. 1972 (1873) FOUR-DAY STATIC FISH TOXICITY STUDIES WITH AROCLOR 1221, AROCLOR 5432, AROCLOR 5442, AROCLOR 5460, AND MCS 1016 IN BLUEGILLS AND CHANNEL CATFISH John Hamlin, Industrial BIO-TEST Laboratories, Inc.	3 types of assay: 1) test material and fish exposure; 2) blank exposure (without fish) ; 3) control exposure (without test material) . Aroclor 1221 (bluegill) : TL50=0.23 ppm. Aroclor 1221 (channel catfish) : TL50=3.34 ppm. Aroclor 5432 (bluegill) : TL50= >100.0 ppm. Aroclor 5432 (channel catfish) : TL50=>100.0 ppm. Aroclor 5442 (bluegill) : TL50= >100.0 ppm. Aroclor 5442 (channel catfish) : TL50=>100.0 ppm. Aroclor 5460 (bluegill) : TL50= >100.0 ppm. Aroclor 5460 (channel catfish) : TL50=>100.0 ppm. MCS 1016 (bluegill) : TL50=0.65 ppm. MCS 1016 (channel catfish) : TL50=0.75 ppm	Aroclor 1221, Aroclor 5432, Aroclor 5442, Aroclor 5460, MCS 1016. Determining TL50
108. 1972 (1902) TOXICOLOGICAL INVESTIGATION OF: MCS 1230 GERMAN MINE FLUID—Lot: OR 162483. Melvin Birch, Younger Laboratories, Inc.	Acute oral and skin absorption minimal lethal dose, as well as skin irritation, eye irritation, vapor inhalation. Acute oral MLD (rat) : >10 g/kg and <12.6 g/kg. Acute skin absorption MLD (rabbit) : >7.9 g/kg. Skin irritation (rabbit) : non-irritating. Eye irritation (rabbit) : slight irritant. Vapor inhalation, ambient temp (rat) : nontoxic. Vapor inhalation, 150°C (rat) : nontoxic.	MCS 1230
109. 1972 (1911) MUTAGENIC STUDY WITH AROCLOR 1260 IN ALBINO MICE. Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg. Mating indices, implantation site, resorption sites, embryos, and mutation rates were unchanged.	Aroclor 1260
110. 1972 (1928) MUTAGENIC STUDY WITH AROCLOR 1254 IN ALBINO MICE. Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg. Mortality: 3 rats treated with 1 g/kg died within 2 days, and 2 control rats died over course of study. Mating index: somewhat low for 1.0 mg/kg at 4 and 6 weeks. Autopsy and mutation: no changes.	Aroclor 1254
111. 1972 (1944) MUTAGENIC STUDY WITH AROCLOR 1242 IN ALBINO MICE.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg.	Aroclor 1242

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	No change in ability of males to mate with or fertilize untreated males, mutation indices, or dominant lethality.	
112. 1972 (1962) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH MCS 1016 IN BEAGLE DOGS. Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	90-day subacute oral toxicity at 1) 1 ppm (days 1–28) to 30 ppm (days 29–90) ; 2) 10 ppm (days 1–28) to 300 ppm (days 29–90) ; and 3) 100 ppm. Results: No changes in body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, or histopathologic studies.	MCS 1016. Measured body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, and histopathologic studies.
113. 1972 (2017) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH MCS 1016 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. Paul Wright, James Plank and M.L. Keplinger reviewed study.	90 days feeding of rats at 30 ppm, 100 ppm, and 300 ppm. Results: significant elevation in liver weights and ratios for female rats feed 300 ppm. No other changes in body weight, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, or gross and microscopic pathologic studies.	MCS 1016. Measured body weight, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, and gross and microscopic pathologic studies.
114. 1972 (2049) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH AROCLOR 1221 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. Paul Wright, James Plank and M.L. Keplinger reviewed study.	90-day feeding of rats at 10, 100, and 300 ppm. Results: no changes in body weight gain, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, gross and microscopic pathologic studies, or organ weights or ratios.	Aroclor 1221.
115. 1972 (2081) TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH MCS 1016 IN WHITE LEGHORN CHICKENS. Dale Fletcher, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Toxicity, reproduction, and residue study. Chickens fed 1, 3, or 10 ppm compound. Results. Mortality: 6 females deaths: 1 control, 2 in 1 ppm group, 1 in 3 ppm group, and 2 in 10 ppm group. No abnormalities or systemic signs of toxicity attributable to MCS 1016. Egg production and quality was normal. Hatchability in 3 ppm group was lower than control, 1 ppm, and 10 ppm groups. No differences in specific gravity and shell thickness of eggs. No differences in body weight, viability of chicks, or gross pathologic changes in chicks.	MCS 1016
116. 1972 (2109) TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH AROCLOR 1221 IN WHITE LEGHORN CHICKENS. Dale Fletcher, Industrial BIO-TEST Laboratories, Inc.	Toxicity, reproduction, and residue study in chickens. Doses of 1 ppm, 3 ppm, and 10 ppm. Results. Body weights, food consumption, gross pathology, and systemic signs of toxicity are normal. Egg production was lower for control birds, and percentage of defective eggs was greater in the control group. No differences in specific gravity and shell thickness. Hatchability	Aroclor 1221

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
M.L. Keplinger	of eggs was slightly lower in the 10 ppm than for the other groups.	
<p>117. 1972 (2137)</p> <p>FOUR-DAY FISH TOXICITY STUDIES WITH AROCLOR 1242, AROCLOR 1254, AND AROCLOR 1260 IN BLUEGILLS AND CHANNEL CATFISH.</p> <p>Kenneth Ebbens, Industrial BIO-TEST Laboratories, Inc.</p> <p>M.L. Keplinger</p>	<p>4-day fish toxicity studies in 3 bioassay conditions: 1) Aroclor and fish; 2) blank (no fish) ; and 3) control (fish but no aroclor) .</p> <p>Results. Aroclor 1242 (bluegill) : TL50=0.24 ppm. Aroclor 1242 (channel catfish) : TL50=0.13 ppm. Aroclor 1254 (bluegill) : TL50= >100.0 ppm. Aroclor 1254 (channel catfish) : TL50=0.20 ppm. Aroclor 1260 (bluegill) : TL50=>100.0 ppm. Aroclor 1260 (channel catfish) : TL50=>100.0 ppm.</p>	Aroclor 1242, Aroclor 1254, Aroclor 1260.

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ADM 005446- ADM 005472
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MONS 002720

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1946

Effect of Cooking on the DDT Content of Beef

R. H. CARTER, P. E. HUBANKS, and H. D. MANN
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1943

The Chemistry of DDT

by H. L. HALLER and RUTH L. BUSBEY

1944

NOVEMBER 24, 1944

SCIENCE

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TOXICITY OF DICHLORO-DIPHENYL-TRICHLORETHANE (DDT) TO GOLD-FISH AND FROGS

In the course of pharmacological studies of 2,2, bis (p-chlorophenyl) 1,1,1 trichlorethane¹ (DDT) the writers have noted that this substance is more toxic to goldfish and frogs than rats, cats and rabbits in terms of the lethal doses recently reported by Smith and Stohlman² (150 mgs/Kg for rats; 200 to 300 mgs/Kg for cats; and 300 mgs/Kg for rabbits, when given intragastrically in olive oil).

Single doses of DDT dissolved in olive oil and incorporated in food pellets, when swallowed by 6 to 10 gm goldfish, were lethal in amounts ranging from 63 to 200 mgs/Kg. Within this range the total mortality was approximately 55 per cent, the number of deaths being correlated roughly with the size of the dose. Death followed these single ingestions of DDT in 24 hours to 6½ days, the onset of the symptoms of poisoning being delayed in some cases for more than four days. The fish became hyperirritable at first and subsequently developed muscular incoordination, muscu-

lar spasms and finally marked prostration, during which phase the fish lay on its side, breathing irregularly and at times making convulsive movements. The incoordination and prostration in some cases persisted for 3 days or more before death. The gross picture of the DDT poisoning resembled that produced by phenol or picrotoxin.

All frogs receiving DDT dissolved in olive oil, by injections into the dorsal lymph sac were all killed in 4 to 72 hours by single doses of 150 mgs/Kg. Some frogs died following injection of quantities as small as 10 mgs/Kg.

These findings that these two cold-blooded aquatic vertebrates are even more sensitive to single doses of DDT than the common laboratory mammals are of interest in connection with the proposed use of DDT in regions where malaria is endemic against the larvae of the mosquito vectors of that disease.

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Jenkins, R.L.; McCollough, R.; Booth, C.F. (1930). "Syntheses in the Diphenyl Series." Industrial and Engineering Chemistry, Vol. 22, p. 31.

January, 1930

INDUSTRIAL AND ENGINEERING CHEMISTRY

Syntheses in the Diphenyl Series^{1,2}

Russell L. Jenkins, Rogers McCullough, and C. F. Booth

FEDERAL PHOSPHORUS COMPANY, ANNISTON, ALA.

Stability of DDT and Related Compounds

BY ELMER E. FLECK AND H. L. HALLER

AUGUST 17, 1945

SCIENCE

177

ACCUMULATION OF DDT IN THE BODY FAT AND ITS APPEARANCE IN THE MILK OF DOGS¹

THE high lipoid-water distribution ratio of DDT suggested that it might be preferentially stored in the adipose tissues of mammals fed DDT. The toxicological behavior of this compound pointed also to possible deposition in body fat. Such a preferential distribution was first indicated by feeding the dibrom analogue of DDT, 2,2-bis(p-bromophenyl)-1,1,1-trichloroethane, to rats and rabbits and determining the increase in tissue levels of bromine. The rise in the

American Journal of Public Health *and* **THE NATION'S HEALTH**

Official Monthly Publication of the American Public Health Association

Volume 36

June, 1946

Number 6

TAKING STOCK OF DDT

On the other side of the ledger Dr. Bishopp reviews the possible dangers which may be involved in the wide and indiscriminate use of this new insecticide. DDT is definitely toxic to man and the domestic animals, although less so than nicotine and certain arsenicals commonly used for similar purposes. It must not be allowed to get into foods or to be accidentally ingested, and must not be applied

to the skin in an oil solution. Therefore, it is important that the suggestions of the Insecticide Division of the Department of Agriculture with regard to standardization and labelling be enforced; and that DDT sprays be not used on cabbage or similar vegetables after the heads have formed, or on crops to be fed to stock, until more is known of their limits of tolerance.

The uses of DDT in public health will not, in general, be such as to threaten the wide disturbances of the balance of nature which have been anticipated by some timid souls. But the application of this substance to extensive areas of swamp land for mosquito control and—still more—its indiscriminate use in the control of agricultural pests, might have more far-reaching effects. The question whether the honey-bee and other beneficial insects may be destroyed is a pertinent

SCIENCE, April 2, 1948, Vol. 107

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Effect of Cooking on the DDT Content of Beef

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THE CHRONIC ORAL TOXICITY OF DDT (2,2-BIS
(p-CHLOROPHENYL-1,1,1-TRICHLOROETHANE)¹

O. GARTH FITZHUGH AND ARTHUR A. NELSON

*From the Division of Pharmacology, Food and Drug Administration,
Federal Security Agency, Washington, D. C.*

Received for publication September 14, 1946

[212] Canadian Journal of Comparative Medicine Tolerance of Turkeys to DDT

August, 1946
Vol. X—No. 8

Report upon Experiments Conducted to
Establish the Tolerance of Turkeys
to DDT

BY A. A. KINGSCOTE, AND C. H. JARVIS*

THE RELATIONSHIP BETWEEN THE LIPOID AFFINITY AND THE
INSECTICIDAL ACTION OF 1,1-bis (p-FLUOROPHENYL) 2,2,2-TRI-
CHLOROETHANE AND RELATED SUBSTANCES¹

S. KIRKWOOD AND P. H. PHILLIPS

*From the Department of Biochemistry, College of Agriculture, University of
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Received for publication April 28, 1946

The Pharmacology of DDT

By ARNOLD J. LEHMAN

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Federal Security Agency, Washington, D.C.*

The Solubility of DDT

	Grams per 100 g. solvent
1. Cyclohexanone	100-120
2. Benzene	77-106
3. Dioxane	46-100
4. Chloroform	31-96
5. Methylene chloride	84-91
6. <i>o</i> -Dichlorobenzene	63-71
7. Tetrahydronaphthalene	52-71
8. Ethyl acetate	68
9. Xylene	56-62
10. Tetrachloroethane	56
11. Acetone	40-55
12. Tetralin	52
13. Pyridine	51
14. Carbon tetrachloride	18-48
15. Toluene	48
16. Ether	27-45
17. Benzyl benzoate	39-41
18. Dimethyl phthalate	31-33
19. Indalone	29
20. Triton	20
21. Cottonseed oil	9-20
22. Tung oil	10-14
23. Kerosene (vaporizing)	11
24. Fuel oil No. 2	10
25. Sesame oil	10
26. Petroleum ether (100-106°C.) (212-222°F.)	10

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THE INDIAN MEDICAL GAZETTE

[Oct., 1946]

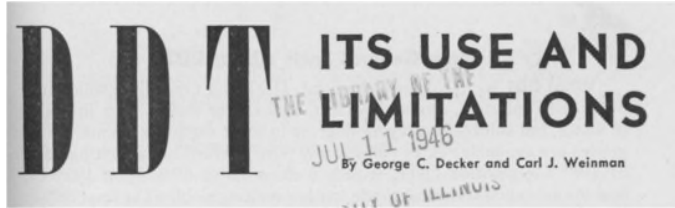
Public Health Section

POISONOUS EFFECTS OF D.D.T. ON HUMANS

By U. CHIT THOUNG, M.Sc. (Lond.), D.I.C.,
A.R.C.S., F.C.S.

Chemical Examiner to the Government of Burma

RECENTLY the writer received a case of food poisoning from the District Health Officer, Bhamo. In this respect two samples of rice were sent to him for examination.



¹ DDT (dichloro-diphenyl-trichloroethane) was first prepared by a German chemist in 1874. However, its insecticidal properties remained unknown until 1939 when Paul Mueller, an employee of the J. R. Geigy Company of Basel, Switzerland, found that it would kill potato beetles. Later he reported its effect on plant lice, moths, and flies. During the past three years entomologists in state, federal, and industrial laboratories have added materially to our knowledge of the usefulness and limitations of this new insecticide.

The use of DDT as an insecticide is covered by a number of Swiss, British, and American patents, all of which are assigned to the J. R. Geigy Company. Many American and foreign companies now manufacture and sell insecticides containing DDT under licenses issued by the Geigy Company.

Received for publication June 2, 1947.

¹ This work was aided by a grant from the American Cyanamid Company.

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THE AMOUNT OF DDT FOUND IN THE MILK OF COWS FOLLOWING SPRAYING¹

D. E. HOWELL, H. W. CAVE, V. G. HELLER, AND W. G. GROSS
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Oklahoma Agricultural Experiment Station, Stillwater*

**2,2-BIS (p-CHLOROPHENYL)-1,1,1-TRICHLOROETHANE (DDT) IN
THE TISSUES OF THE RAT FOLLOWING ORAL INGESTION FOR
PERIODS OF SIX MONTHS TO TWO YEARS¹**

EDWIN P. LAUG AND O. GARTH FITZHUGH

*From the Division of Pharmacology, Food and Drug Administration, Federal Security Agency,
Washington, D. C.*

Received for publication January 8, 1946

**LIVER CELL ALTERATION AND DDT STORAGE IN THE FAT OF
THE RAT INDUCED BY DIETARY LEVELS OF 1 TO 50 P.P.M. DDT¹**

**EDWIN P. LAUG, ARTHUR A. NELSON, O. GARTH FITZHUGH AND
FRIEDA M. KUNZE**

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Received for publication November 17, 1949

New Insecticides and Rodenticides and Their Health Aspects

H. A. Thiemann

To cite this article: H. A. Thiemann (1949) New Insecticides and Rodenticides and Their Health Aspects, American Industrial Hygiene Association Quarterly, 10:1, 10-15, DOI: [10.1080/00968204909344141](https://doi.org/10.1080/00968204909344141)

To link to this article: <https://doi.org/10.1080/00968204909344141>

New Insecticides and Rodenticides and Their Health Aspects

H. A. THIEMANN, Engineer
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A perhaps more important health aspect of DDT is the fact that it is stored in the body fat at a level four to ten times that of the dietary intake. It has been shown to be secreted in the milk of cows, goats, dogs and rats. Other animals fed the milk from the DDT treated animals show toxic symptoms. All the DDT in the milk appears to be concentrated in the butterfat portion, and to be transferred to the butter. Therefore, a relatively small amount of DDT in the whole milk results in a significant amount in the butter. The accumulation of appreciable quantities of DDT in animal tissues at low dietary levels of DDT poses a difficult problem, since many animal products are used for human consumption. This may be especially important in the case of infants and children because of the high consumption of milk.

OBSERVATIONS ON INBRED MICE EXPOSED TO DDT¹

B. E. BENNISON and F. K. MOSTOFI,² *National Cancer Institute, National Institutes of Health, Public Health Service, Bethesda, Md.*

The use of DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl)-ethane) as an insecticide began in 1939 (1), and by 1947 annual production in the U. S. had reached 49.6 million pounds (2). Pharmacologic studies have shown that the chief systemic actions of DDT in animals are (a) central nervous system effects characterized by hyperexcitability, generalized tremors, spastic or flaccid paralysis and convulsions, and (b) hyaline degeneration and focal necrosis of the liver (3, 4). The literature to 1947 has been reviewed by Stammers and Whitfield (5).

Occurrence of DDT in human fat and milk.

EP Laug, FM Kunze, CS Prickett - Arch. Indust. Hyg. & Occupational ..., 1951 - cabdirect.org
Seventy-five samples of fat obtained from different persons at autopsy or during biopsy or abdominal surgery were examined for content of DDT. The DDT content of breast milk from 32 Negro women was estimated. The investigation was planned as a preliminary ...

[Cited by 270](#)[Related articles](#)[All 3 versions](#)

Colorimetric determination of DDT in milk and fatty materials

MS Schechter, MA Pogorelskin, HL Haller - Analytical Chemistry, 1947 - ACS Publications
A procedure has been developed for the determination of DDT as such in foodstuffs containing considerable amounts of fatty matter such as milk, butter, and animal fat. Although the method is not rapid, it permits the detection and determination of DDT in milkin ...

[Cited by 60](#)[Related articles](#)[All 3 versions](#)

Estimation of DDT in milk by determination of organic chlorine

RH Carter - Analytical Chemistry, 1947 - ACS Publications
THE use of DDT as an insecticide on forage and truck crops such as alfalfa, clover, and pea vines, which may be used as feed for livestock, particularly for beef and dairy cattle, has created a need for methods of determining DDT in milk or meat products from these animals. Methods ...

[Cited by 42](#)[Related articles](#)[All 2 versions](#)

Transmission of the Toxicity of DDT through the Milk of White Rats and Goats.

HS Telford, JE Guthrie - Science (Washington), 1945 - cabdirect.org
Three female rats, each with a one-day old litter, were fed with 0.1 per cent. DDT in mash. Typical tremors appeared in the mothers mothers Subject Category: People Groupssee more details between the 6th and the 13th days and in their young between the 14th and ...

[Cited by 46](#)[Related articles](#)[All 9 versions](#)

The effect of feeding alfalfa hay containing DDT residue on the DDT content of cow's milk

JB Shepherd, LA Moore, RH Carter, FW Poos - Journal of Dairy Science, 1949 - Elsevier
Alfalfa treated with 2.4 lb. of DDT per acre, in the form of an aerosol, and fed to cows at the rate of 1 lb. of hay per day per 100 lb. of body weight produced milk containing up to 10.1 γ of DDT per g. or 259.1 γ per g. of butterfat. The daily intake of DDT was as high as 903 mg ...

[Cited by 26](#)[Related articles](#)[All 3 versions](#)

The effect of dosage level and various methods of administration on the concentration of DDT in milk

RE Ely, LA Moore, RH Carter, HD Mann... - Journal of Dairy Science, 1952 - Elsevier
Higher concentrations of DDT in the milk occurred when cows were fed DDT as a residue on field-sprayed alfalfa than when comparable dosages of crystalline DDT were fed, suggesting that possibly intestinal absorption of DDT residues from sprayed forages is more complete ...

[Cited by 29](#)[Related articles](#)[All 3 versions](#)

The DDT content of milk products.

HD Mann, RH Carter, RE Ely - ... of Milk and Food Technology, 1950 - cabdirect.org
see more details were prepared on a pilot-plant scale. The DDT content was determined by the Schechter-Haller colorimetric method. The DDT contents were 7.5 and 150 ppm in the raw whole milk and in the butterfat respectively. The corresponding figures for raw skim milk ...

[Cited by 20](#)[Related articles](#)

[\[PDF\] journalofdairyscience.org](#)

The amount of DDT found in the milk of cows following spraying.

DE Howell, HW Cave, VG Heller, WG Gross - Journal of Dairy ..., 1947 - cabdirect.org

Sixteen Jersey and Holstein cows were sprayed daily or at 14-day intervals with either an emulsion containing 0.25 to 1.0 per cent. or a suspension containing 0.25 to 5.0 per cent. of DDT. The amount of DDT excreted in the milk, estimated colorimetrically ...

[Cited by 16Related articlesAll 3 versions](#)

Secretion of DDT in milk of dairy cows fed low-residue alfalfa hay.

RF Smith, WM Hoskins, OH Fullmer - Journal of Economic ..., 1948 - cabdirect.org

During a period of 3 months 7 dairy cows were given lucerne hay which had been sprayed, 10 days before cutting, with 0-25 lb. DDT in 5 gal. water per acre. The residue of DDT in the hay during feeding was on the average 7 to 8 ppm It was estimated that ...

[Cited by 16Related articlesAll 2 versions](#)

Isolation of DDT from fats.

B Davidow - Journal of the Association of Official Agricultural ..., 1950 - cabdirect.org

A chromatographic method is described for extracting DDT from butterfat using a column of ceelite (a diatomaceous earth) impregnated with an H₂SO₄-fuming H₂SO₄ mixture and slurried with carbon tetrachloride. SEI.

[Cited by 78Related articles](#)

of milk from cows fed pea vine silage containing DDT residues.

RH Carter, PE Hubanks, HD Mann... - Journal of economic ..., 1949 - cabdirect.org

In 1946 chemical analyses were made to determine the DDT content of red vines and silage from fields treated with DDT sprays, dust, and aerosols'. The DDT content in milk from cows fed silage from pea vines that had been treated with Freon-propelled aerosols ...

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DDT residues in agricultural products

RH Carter - Industrial & Engineering Chemistry, 1948 - ACS Publications

... **DDT** content of **milk** from cows fed silage containing **DDT** residues ... **DDT** CONTENT OF **MILK**

In a cooperative experiment with the University of Maryland, cows were fed pea-vine silage at the rate of 3 pounds per 100 pounds of animal for 2 months ...

[Cited by 18Related articles](#)

Fly control and milk flow.

WN Bruce, GC Decker - Journal of Economic Entomology, 1947 - cabdirect.org

Two dairy herds in Illinois were treated three times during the season at intervals of three or four weeks for the control of flies with a spray containing water-wettable DDT, applied at the rate of 28 gm. DDT per cow, two others were similarly treated with Rhothane (dichlordiphenyldichlo ...

[Cited by 21Related articlesAll 3 versions](#)

Use of DDT insecticides on food products

OG Fitzhugh - Industrial & Engineering Chemistry, 1948 - ACS Publications

... symptoms. All the **DDT** in the milk appearsto be concentrated in thebutterfat portion and to be transferred to thebutter {6}; therefore, a relatively small amount of **DDT** in the whole **milk** resultsin a significant amount in the butter ...

[Cited by 27Related articles](#)

Toxicity of DDT to laying hens

M Rubin, HR Bird, N Green, RH Carter - Poultry Science, 1947 - academic.oup.com

... & Eng. Chem., Anal. Ed. 17: 704-709. Telford, Horace S., and James E. Guthrie, 1945. Transmission of the toxicity of **DDT** through the **milk** of white rats and goats. Science 102: 647. Umhoefer, Robert R., 1943. Determination of halo- gens in organic compounds. Ind. and Eng ...

[Cited by 35Related articles](#)

Survey analyses of human milk and fat for DDT content.

EP Laug, CS PRICKETT, FM KUNZE - ... Proceedings. Federation of ..., 1950 - cabdirect.org

The DDT concentrations in the milk of 24 women, some of whom occasionally used household DDT sprays, ranged from 0 to 0.77 (average 0.14) ppm GFS.

[Cited by 9Related articles](#)

[Methoxychlor, DDT, CS-708 and Dieldrin their Rates of Excretion in Milk.](#)

HV Claborn, RW Wells - Agric. Chem., 1952 - cabdirect.org

Jersey cows in Texas were sprayed once with a suspension of DDT, methoxy-DDT (methoxychlor) or CS-708 (a 1: 2 mixture of I, I-bis(p-chlorophenyl)-2-nitropropane and 1, 1-bis(p-chlorophenyl)-2-nitrobutane) or an emulsified solution of ...

[Cited by 8Related articles](#)

[Contamination of milk from DDT sprays applied to dairy barns.](#)

HV Claborn, HF Beckman, RW Wells - Journal of Economic ..., 1950 - cabdirect.org

Up to 1-4 ppm DDT were secreted in the milk of cows after spraying dairy barns with this insecticide. Contamination was probably due to spray residues on the feeding troughs as it did not occur when the troughs were covered during spraying or were washed ...

[Cited by 7Related articlesAll 3 versions](#)

[DDT poisoning—A new syndrome with neuropsychiatric manifestations](#)

MS Biskind, I Bieber - American journal of psychotherapy, 1949 - Am Psychiatric Assoc

... According to the TJ. 8. Department of Agriculture (56), **milk** from cattle sprayed with the minimum concentration of **DDT** in use (0.5 per ... Telford, HS, and Guthrie, JE: Transmission of the Toxicity of **DDT** Through the **Milk** of White Eats and Goats, Science, 102: 647, Dec. 21, 1945 ...

[Cited by 19Related articlesAll 4 versions](#)

[\[PDF\] journalofdairyscience.org](#)

[The effect of various dosage levels of crystalline lindane on the concentration of lindane in cow's milk](#)

RE Ely, LA Moore, HD Mann, RH Carter - Journal of Dairy Science, 1952 - Elsevier

... Comparison of the concentrations of lindane in the **milk** with the concentration of **DDT** in **milk** (3) indicates that approximately the same amounts are excreted in the **milk** when comparable intakes are given. This is clearly evident ...

[Cited by 13Related articlesAll 2 versions](#)

[rocarbon content of milk from cattle sprayed for control of horn flies.](#)

RH Carter - Journal of economic entomology, 1949 - cabdirect.org

The amount of chlorinated hydrocarbons, if any, in milk produced by cows sprayed for the control of Siphona irritans[Haematobia irritans], L., with water suspensions of commercial wettable powders containing them was investigated in Texas between May and September 1947. The ...

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[\[PDF\] nih.gov](#)

[The control of rat fleas \(Xenopsylla cheopis\) by DDT](#)

DE Davis - Pub. Health Rep, 1945 - ncbi.nlm.nih.gov

... The use of **DDT** to reduce the number of rat fleas is a practical procedure which may be useful in control of typhus fever ... OUTBREAKS OF DISEASE IN THE UNITED STATES DURING 1943, TRANSMITTED BY WATER, **MILK** AND **MILK** PRODUCTS, AND OTHER FOODS ...

[Cited by 21Related articlesAll 4 versions](#)

[Effect of DDT on Dairy Cattle and Milk.](#)

CW Wingo, OS Crisler - Journal of Economic Entomology, 1948 - cabdirect.org

see more details [cf. RAE, B 36 105-106] after being sprayed for the control of flies.

Technical **DDT** was administered to the two test animals by means of capsule and balling gun each day except the four Sundays for 29 days, and they received the standard ration of ...

[Cited by 5Related articlesAll 2 versions](#)

Experiments with peas and sweet corn treated with DDT insecticides

HA Lardy - Industrial & Engineering Chemistry, 1948 - ACS Publications

... **DDT** in **Milk** of Cows Fed on Dusted Pea Vine Silage PPM **DDT** in **Milk** Days on Expt. From cow 500 From others 75 0.3 82 0.0 ". 116 0.4 0.3 120 0.1∞ 135 ".2 ... ∞ Colostrum sample ... Table V. **DDT** in **Milk** from Cows Fed Corn Silage Containing 5 10 PPM **DDT** Days on Expt ...

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Excretion of DDT and TDE in Milk from Cows treated with these Insecticides.

HV Claborn, HF Beckman, RW Wells - Journal of Economic ..., 1950 - cabdirect.org

see more details or I, I-dichloro-2, 2-bis (parachlorophenyl) ethane [DDD] in emulsion concentrates diluted to contain 0.5 per cent. insecticide. Four dairy herds were treated with **DDT** and three with DDD, and at the beginning of the tests and sometimes subsequently ...

[Cited by 5 Related articles](#)[All 3 versions](#)

Effect of treatment of dairy pastures with BHC and DDT on the flavour and composition of milk, cream, and butter.

FH McDowall, MR Patchell, F Hurst... - New Zealand Journal of ..., 1955 - cabdirect.org

see more details. Treatment with commercial BHC containing 10 per cent. γ-isomer at 20 lb. per acre caused a slight taint in **milk**, butter and cream. Treatment of wet pastures with both insecticides insecticides Subject Category: Miscellaneoussee more details and with ...

[Cited by 5 Related articles](#)

[PDF] journalofdairyscience.org

Feeding DDT and alfalfa sprayed with DDT to calves

JW Thomas, PE Hubanks, RH Carter, LA Moore - Journal of Dairy Science, 1951 - Elsevier

... Mice. Proe. Soc. Exptl. Biol., Med., 66: 642-645. 1947. (8) SCHECHTER~ MS~ POGORELSKIN, MA~ AND HALLER, HL Colorimetric Determinations of **DDT** in **Milk** and Fatty Materials. Anal. Chem., 19: 52-53. 1947. (9) WILSON ...

[Cited by 10 Related articles](#)[All 3 versions](#)

DDT Toxicity.

HS Telford - Soap and sanitary Chemicals, 1945 - cabdirect.org

An account is given of tests noticed in more detail elsewhere [RAE, a 36 379] to determine the toxicity of **milk**, cream and butter from goats that had received oral doses of **DDT** [cf. B 35 193]. The whole **milk** of a goat that received 0.68 gm. **DDT** per lb ...

[Cited by 6 Related articles](#)

The transfer of DDT from the feed to eggs and body tissues of white leghorn hens

CI Draper, JR Harris, DA Greenwood... - Poultry ..., 1952 - academic.oup.com

... 1950. **DDT** in **milk** and tissues of dairy cows fed **DDT**-dusted alfalfa hay. Advances in Chem., Series 1:237-243 ... Therap. 98: 268-273. Schechter, MA, MA Pogorelskin and HL Haller. 1947. Colorimetric determination of **DDT** in **milk** and fatty materials. Anal. Chem. 19: 51- 53 ...

[Cited by 22 Related articles](#)[All 2 versions](#)

Degradation of DDT by resistant and susceptible strains of house flies

J Sternburg, CW Kearns - Annals of the Entomological Society of ..., 1950 - academic.oup.com

... 447 flies were allowed to feed on **milk** containing 2 mg. of **DDT** per ml. of **milk** ... TABLE III RECOVERY OF **DDT** AND DDE FROM POOLED TISSUES DISSECTED FROM 20 RESISTANT FLIES 15 HOURS AFTER FEEDING ON **MILK** CONTAINING 2 MG. **DDT** PER ML ...

[Cited by 64 Related articles](#)[All 3 versions](#)

ent in the fly food on the resistance to DDT

GG Mer, W Furmaska - Rivista di Parassitologia, 1953 - cabdirect.org

These experiments were carried out with a laboratory strain of *Musca domestica*: the lethal dose of **DDT** was well known and was stable. The control adults were given water to drink and cane sugar plus whole **milk** powder as food. The experimental adults were...

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[\[PDF\] nih.gov](#)

Toxic effects of DDT in man

RAM Case - British medical journal, 1945 - ncbi.nlm.nih.gov

... in vitamins A and C. The protein content of the children's diet was inadequate, owing in large measure to the fact that no **milk** was available for ... TOXIC EFFECTS OF 2,2-bis (p-CHLORPHENYL) 1,1,1-TRICHLOROETHANE (**DDT**) IN MAN BY RAM CASE, Ph.D., MB, Ch.B. (From the ...

[Cited by 45](#)[Related articles](#)[All 8 versions](#)

Determination of DDT in Milk produced in Barns sprayed with DDT Insecticides.

HJ Harris, EJ Hansens, CC Alexander - Agric. Chew., 1950 - cabdirect.org

The following is based on the authors' introduction and summary. In view of a report that DDT could be found in milk as a result of the application of the insecticide to dairy barns, and of a recommendation by the United States Department of Agriculture ...

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Contamination of meat and milk by chlorinated hydrocarbon insecticides used for livestock pest control.

RC Bushland, HV Claborn, HF Beckman... - Journal of Economic ..., 1950 - cabdirect.org

... United States on the effects of sprays and dips of **DDT**, DDD (TDE [dichlorodiphenyldichloroethane]), methoxy-**DDT** (methoxychlor), chlordan, toxaphene, technical BHC (benzene hexachloride) and lindane [containing at least 99 per cent. γ BHC] on the meat and **milk** of treated ...

[Cited by 15](#)[Related articles](#)[All 3 versions](#)

The Effectiveness of DDT as a residual Spray against Houseflies.

AW Lindquist, AH Madden, HG Wilson... - Journal of Economic ..., 1944 - cabdirect.org

Some results are given of studies begun in Florida in February 1943 in which it was found that DDT, applied as, a spray in a suitable solvent, remains as a nearly invisible deposit after the liquid has volatilised and acts as a residual contact insecticide against house-flies [*Musca domestica* ...

[Cited by 18](#)[Related articles](#)[All 2 versions](#)

The Effect of Dosage Level and Method of Administration of DDT on the Concentration of DDT in Milk.

RE Ely, LA Moore, RH Carter, HD Mann... - ... of **DDT** in **Milk**., 1950 - cabdirect.org

These papers, of which the first is virtually a summary of the second, contain the results of experiments in which DDT was administered by various methods and in different quantities to healthy cows that were fed and milked twice daily. Crystalline DDT as ...

[Cited by 3](#)[Related articles](#)

The effect on cattle of long-continued cutaneous applications of DDT.

WJ Roulston, LF Hitchcock, AW Turner... - Australian Journal of ..., 1953 - CSIRO

... Anal. Ed. 17: 704-9. SCHECHTER, MS, POWRELSKIN, M. A., and HAL-ER, HL (1947).-Colorimetric determination of **DDT** in **milk** and fatty material. Anal. Chem ... C. M. (1945).-Accumulation of **DDT** in the body fat and its appearance in the **milk** of dogs. Science 102 ...

[Cited by 6](#)[Related articles](#)[All 4 versions](#)

The penetration of the insect cuticle by DDT and related compounds

G Armstrong, FR Bradbury... - Annals of Applied ..., 1952 - Wiley Online Library

... It was found subsequently that this unpleasant and time-consuming operation could be successfully avoided by modification of the method used by Davidow (1950) for the separation of **DDT** from fat in the analysis of **DDT** in **milk** samples ...

[Cited by 18](#)[Related articles](#)[All 2 versions](#)

[Feeding experiments with **DDT**-treated pea vine silage with special reference to dairy cows, sheep and laboratory animals.](#)

HF Wilson, NN Allen, G Bohstedt, J Bethel... - Journal of economic ..., 1946 - cabdirect.org
No adverse effect was noted when pea vine silage, treated in the silo with DDT at the rate of 1 lb. per ton of fresh vines, was fed to 5 cows for 4 to 5 months. No change in any blood constituent was observed, though appreciable quantities of DDT could be demonstrated in the liver ...

[Cited by 17](#)[Related articles](#)[All 4 versions](#)

[**DDT** Developments. Further Light on recent **DDT** Failures against the House Fly-**DDT** Bans discussed.](#)

EF Knipling - Soap and sanitary Chemicals, 1949 - cabdirect.org
Since the Food and Drug Administration of the United States has pronounced that the presence of **DDT** in **milk** will be considered contrary to the provisions of the Food, Drug and Cosmetic Act, the Bureau of Entomology and Plant Quarantine has changed its recommendations ...

[Cited by 4](#)[Related articles](#)[All 2 versions](#)

[lem](#)

JC Leary, WI Fishbein, LC Salter - 1946 - krishikosh.egranth.ac.in
Page 1. **DDT** and the Insect Problem Page 2. **DDT** and the Insect Problem JAMES C. LEARY Former Science Editor, Chicago Daily News WILLIAM I. FISHBEIN, BS, MD Epidemiologist, Chicago Board of Health LAWRENCE C. SALTER ...

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[\[PDF\] aphapublications.org](#)

[\[PDF\] Present position of **DDT** in the control of insects of medical importance](#)

FC Bishopp - American Journal of Public Health and the ..., 1946 - ajph.aphapublications.org
... 7. Following ingestion in appreciable quantities, **DDT** is excreted in the **milk**, presumably associated with the fat globules. 10 11 8. **DDT** is a nerve poison, as indicated by the early appearance of muscular tremors and other symptoms ...

[Cited by 27](#)[Related articles](#)[All 5 versions](#)

[The storage of **DDT** in the tissues of pigs fed beef containing this compound](#)

RH Carter, PE Hubanks, HD Mann... - Journal of animal ..., 1948 - academic.oup.com
... Beef from the carcasses of three steers which had been fed for a number of months on hay containing **DDT** residues, and of two calves which had been raised on **milk** from cows on similar feed, was used as a supplement to corn meal in these tests ...

[Cited by 14](#)[Related articles](#)[All 3 versions](#)

[\[PDF\] aphapublications.org](#)

[\[PDF\] Present status of our knowledge of **DDT** intoxication](#)

WJ Hayes Jr - American Journal of Public Health and the ..., 1955 - ajph.aphapublications.org
... p-p'-isomer. **DDT**-derived material is excreted in man in urine, feces, and **milk**. Animal studies have indicated that **DDT** occurs in the secretion of the skin and that it passes the placental barrier into the fetus. The absorption and ...

[Cited by 32](#)[Related articles](#)[All 5 versions](#)

[Determination of **DDT** by bioassay.](#)

C Pagan, RH Hageman - Science (Washington), 1950 - cabdirect.org

A method is described in which guppies (*Lebistes reticulatus*[*Poecilia reticulata*]) are used in the bio-assay of DDT. Mortality counts after 24 hours in concentrations from 0.025 to 0.200 part per million of technical DDT in water ranged from 15 to 90 per cent., and the data gave a straight ...

[Cited by 4](#)[Related articles](#)[All 8 versions](#)

Agricultural Applications of DDT, with special Reference to the Importance of Residues.

GC Decker - *Journal of economic entomology*, 1946 - [cabdirect.org](#)

The author discusses the possible injurious effects on man or domestic animals of DDT residues on plants, with special reference to the United States. He points out that there is little or no risk in using DDT on plants of which no part is used as food or fodder, on such crops as potato ...

[Cited by 12](#)[Related articles](#)[All 4 versions](#)

DDT in milk following barn spraying.

DEH Frear, WN Bruce, AC Ragsdale - *Journal of Economic ...*, 1950 - [cabdirect.org](#)

An investigation into the extent of contamination of milk from cows housed and fed in barns sprayed with DDT [cf. RAE, B 39 81] was carried out in 1949 in four barns in Pennsylvania, three in Illinois and one in Missouri. A suspension containing 10 lb. of ...

[Cited by 2](#)[Related articles](#)[All 3 versions](#)

DDT poisoning and the elusive "virus X:" A new cause for gastro-enteritis

MS Biskind - *The American journal of digestive diseases*, 1949 - Springer

... 15. W.oodard, G., Ofner, Ruth B., and Montgomery, CM: Accumulation of **DDT** in the body fat and its appearance in the **milk** of dogs ... 16. Telford, HS, and Guthrie, JB: Transmission of the toxicity of **DDT** throug~ll the **milk** of white rats and goats, *ibid.*, 102:647, Dec. 21, 1945. 17 ...

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The DDT content of milk from a cow sprayed with DDT.

RH Carter, HD Mann - *Journal of economic entomology*, 1949 - [cabdirect.org](#)

In further work on the amount of DDT in the milk of sprayed cows [cf. RAE, B 38 53], the quantities found in the milk of an Iowa herd thoroughly sprayed with a wettable powder suspension containing 4 lb. DDT per 100 US gals. on 17th July 1948 were ...

[Cited by 2](#)[Related articles](#)[All 4 versions](#)

The Effect of Fly Food on Resistance to Insecticides containing DDT or Pyrethrum.

ER McGowan, WA Gersdorff - *Soap and sanitary Chemicals*, 1945 - [cabdirect.org](#)

An account is given of experiments made to assess the extent to which the resistance of house-flies [*Muscat domestica*, L.] to insecticidal sprays is influenced by the food supplied to the insects before and after treatment, and to determine whether resistance to different insecticides ...

[Cited by 4](#)[Related articles](#)

. 1-Trichloro-2, 2-bis (p-methoxyphenyl) ethane in Milk and Fatty Materials

HV Claborn, HF Beckman - *Analytical Chemistry*, 1952 - ACS Publications

... p- L methoxyphenyl) ethane] for the control of livestock pests (Z, S) made further studies necessary to determine more accurately than has previously been possible the amount of methoxychlor de- posited in fat and excreted in the **milk** of animals ... (S) for separating **DDT** from fats ...

[Cited by 14](#)[Related articles](#)

The control of houseflies by DDT sprays

WC Baker, HI Scudder, EL Guy - *Public Health Reports (1896-1970)*, 1947 - JSTOR

... The investigations covered in this paper were made at **milk** and food establishments to determine the effective duration of **DDT** as a residual spray deposit on surfaces, the amount of treatment necessary to obtain practical control, and the most effective method of appli- cation ...

[Cited by 17](#)[Related articles](#)[All 5 versions](#)

Toxicity of DDT sprays to livestock.

HS Telford, JE Guthrie - Soap and sanitary Chemicals, 1946 - cabdirect.org

Studies on the effect on dairy cows and goats of DDT applied in sprays as emulsified solutions were undertaken in view of the widespread use that is likely to be made of it in sprays, dips and dusts for livestock. Weekly haemoglobin determinations and white and red cell counts on ...

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The toxaphene and chlordane content of milk from cows receiving these materials in their feed

RH Carter, PE Hubanks, FW Poos, LA Moore... - Journal of Dairy ..., 1953 - Elsevier

... (2) CAR-R, RH Estimation of **DDT** in **Milk** by Determination of Organic Chlorine. Ind ... (5) ELY, RE, MOORE, LA, CARTER, RH, AND POOS, FW The **DDT**, Toxaphene and Chlordane Content of **Milk** as Affected by Feeding Alfalfa Hay Sprayed with These Insecticides. USDA, Bur ...

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Death following accidental ingestion of DDT: experimental studies

NJ Smith - Journal of the American Medical Association, 1948 - jamanetwork.com

... 1, 1946. On the afternoon of hat day he drank, accidentally, 120 cc. of a 5 per cent solution of **DDT**. He immediately realized his error and drank a quart of **milk** within a few minutes after swallowing the poison. The patient then drank several glasses of beer ...

[Cited by 33Related articlesAll 2 versions](#)

[\[PDF\] jfoodprotection.org](#)

Membrane Filter Method for Determination of Coliforms in Pasteurized and Certified Milk

R Ehrlich - Journal of **Milk** and Food Technology, 1953 - jfoodprotection.org

... Ibid, 7, 31-40 (19:36). 8. Schechter, MS, Pogorelskin, :f. A., and Haller, HL Colorimetric DP-termination of **DDT** in **Milk**. Agr. Chem., Oct. (1946). 9. Schechter, MS, Pokorelskin, M. A .. and Haller, H. L. Colorimetric Determin- ations of **DDT** in **Milk** and Fatty Mater- ials. Ind. Eng ...

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DDT to control insect pests affecting livestock.

WG Bruce, EB Blakeslee - Journal of economic entomology, 1946 - cabdirect.org

The following is based on the authors' summary of this account of experiments made in 1944 and 1945 on the effectiveness of DDT for the control of various Arthropod pests of livestock (mostly cattle) in the south-eastern United States. A serious outbreak of Stomoxys calcitrans, L ...

[Cited by 8Related articlesAll 4 versions](#)

DDT-resistance in House Flies. Experience at Roseworthy Agricultural College.

RN McCulloch - Journal of the Department of Agriculture of South ..., 1955 - cabdirect.org

DDT gave good control of house-flies (Musca domestica L.) at Roseworthy Agricultural College, South Australia, in 1947-50, but populations then began to rise again. The piggery was sprayed twice with DDT and twice with BHC in the spring of 1952, but populations were so great ...

[Cited by 4Related articles](#)

Effect of coconut milk on the growth in vitro of plant virus tumor tissue

LG Nickell - Botanical Gazette, 1950 - journals.uchicago.edu

... 1950. 6. S1WITH, FF; BRIERLY, P.; and FULTON, RA Response of some plants to **DDT**, hexaethyl tetraphosphate, and parathion applied as aero- sols ... 1947- EFFECT OF COCONUT **MILK** ON THE GROMITH IN VITRO OF PLANT VIRUS TUMOR TISSUE LOUIS G. NICKELL ...

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Effect of feeding DDT dusted alfalfa hay to fattening lambs

LE Harris, T Myint, C Biddulph... - Journal of Animal ..., 1951 - academic.oup.com

... **DDT** accumulates in the fatty tissue and **milk** of dairy cows (Bid- dulphe et al., 1950) as well as the fatty tissue and eggs of chickens (Bryson et al., 1950) ... 1950. **DDT** in **milk** and tissues of dairy cows fed **DDT**-dusted alfalfa hay. Advances in Chem. Series No. 1 pp. 237 ...

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cell alteration and **DDT** storage in the fat of the rat induced by dietary levels of 1 to 50 ppm **DDT**.

EP Laug, AA Nelson, OG Fitzhugh... - ... of Pharmacology and ... , 1950 - cabdirect.org

1. Accumulation of DDT in the fat occurs at every level of intake, down to and including 1 ppm. Greater storage is favoured in the female. " 2. With time there is a progressive rise in storage, reaching a maximum at 19 to 23 weeks. "3. The age of the animal does not appear to affect ...

[Cited by 122Related articlesAll 6 versions](#)

Studies on the resistance of insects to insecticides. I. Cholinesterase in house flies (*Musca domestica* L.) resistant to **DDT**

FH Babers, JJ Pratt Jr - Physiological Zoology, 1950 - journals.uchicago.edu

... flies were reared in the labora- tory on standard larval medium (Anon., 1949), and the adults were fed the gela- tin-'milk' formula' in use at the laboratory of the Bureau of Entomology and Plant Quarantine, at Orlando, Florida. The col- ony of flies resistant to **DDT** was started from ...

[Cited by 37Related articlesAll 4 versions](#)

Toxicity of **DDT**: a Report on. Experimental Studies.

PA Neal, WF Von Oettingen - Soap, 1946 - cabdirect.org

This is one of the best summaries of the DDT toxicity problem that has so far appeared. Some of the new facts and opinions are worthy of comment. 1. The most effective solvents for DDT possess physico-chemical properties which often lead to irritation of the skin and mucous ...

[Cited by 4Related articles](#)

DDT resistance in Korean body lice.

HS Hurlbut, RM Altman, C Nibley Jr - Science (Washington), 1952 - cabdirect.org

To combat lousiness in a large group of Korean troops, 10 per cent. DDT powder was applied weekly throughout the winter and spring of 1951; but nevertheless, infestation steadily increased. By May, the fifth month of routine application, over 34, 000 lb. of powder had been used ...

[Cited by 62Related articlesAll 6 versions](#)

Analysis of a **DDT**-resistant strain of *Drosophila*.

JF Crow - Journal of Economic Entomology, 1954 - cabdirect.org

In an attempt to duplicate to some extent the conditions under which strains of insects develop resistance to DDT in nature, *Drosophila* was bred in cages in which DDT was applied to the inside surface in concentrations that were increased at irregular intervals over a period of three ...

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[\[PDF\] egranth.ac.in](#)

[\[book\] Ddt Killer Of Killers](#)

OT Zimmerman, I Lavine - 1946 - krishikosh.egranth.ac.in

... **DDT** used in dairy barns and on cattle re,lucss the fly population and results in an increased yielel of **milk**. The Female of the Species ... 117 22. Cows kept free from flies by direct application of **DDT** will give from 3 to 8% more **milk** than their untreated sisters. 118 23 ...

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Comparative Effectiveness of **DDT** and **DDD** for Control of Flies.

HL Sweetman - Journal of Economic Entomology, 1947 - cabdirect.org

During 1946, sprays prepared from 25 per cent. emulsion concentrates of DDD [dichlordiphenyldichlorethane] and DDT were compared for the control of flies on two dairy herds of about 60 cows each in Massachusetts. Horn flies [*Siphona irritans*[*Haematobia irritans*], L.] ...

[Cited by 4Related articles](#)

The fate of labelled insecticide residues in food products. I.—
Studies with a radioactive bromine analogue of DDT

FPW Winteringham, A Harrison... - Journal of the ..., 1950 - Wiley Online Library
... I.-Studies with a Radioactive Bromine Analogue of **DDT** By FPW WINTERINGHAM,t A.
HARRISON,t C. R. JONES,\$ JL McGIRRS and WH TEMPLETON11 ... (11) of the normal insecticide
DDT (I). Hansen, Hansen and (p-CIC,H,),CHCCI, (p-BrC,H,),CHCCI, (p-CIC,H,),C:CCI ...

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DDT as a spot treatment for flies.

HL Sweetman - Journal of economic entomology, 1946 - cabdirect.org
Tests in Massachusetts have shown that under local conditions, DDT sprays for the control of
flies need not be applied indiscriminately over extensive areas but only to favoured resting places.
A solution of 5 per cent. DDT in odourless kerosene applied in this way gave adequate ...

[Cited by 3](#)[Related articles](#)[All 5 versions](#)

Resistance of houseflies to DDT.

FPW Winteringham, PM Loveday, A Harrison - Nature, 1951 - cabdirect.org
Recently, American workers have shown that DDT can be rapidly metabolized to an inactive
compound in the milkweed bug (*Oncopeltus fasciatus*); also that DDT-resistant houseflies possess
this power of metabolizing DDT to a greater degree than do normal susceptible flies. This ...

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y of DDT

AJ Lehman - Advances in Food Research, 1949 - Elsevier
... by Claborn (1946). The determination of **DDT** in body fat of experiinental animals
and **milk** requires certain modifications of the Schechter procedure before satisfactory
recoveries can be obtained. Samples containing large ...

[Cited by 2](#)[Related articles](#)

DDT and newer persistent insecticides.

TF West, GA Campbell - **DDT and newer persistent insecticides.**, 1950 - cabdirect.org
The second edition of this book with the additional chapters on benzene hexachloride, chlordane
and toxaphene enables those whose work is connected with insecticides to view DDT and the
newer persistent insecticides in a better perspective, and to use them with greater effect ...

[Cited by 42](#)[Related articles](#)[All 3 versions](#)

**Absorption and Metabolism of DDT by resistant and susceptible
House Flies.**

J Sternburg, CW Kearns, WN Bruce - Journal of Economic ..., 1950 - cabdirect.org
Some of the literature on the development of resistance to DDT in *Musca domestica*, L. [cf. RAE,
B 38 187, etc.] is reviewed, and an account is given of an investigation into the possibility that
resistant flies may have developed an abnormal ability to metabolise the compound. The ...

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[\[PDF\] gipe.ac.in](#)

[\[book\] **Milk and food sanitation practice**](#)

HS Adams - 1947 - dspace.gipe.ac.in
Page 1. **Milk** and Food Sanitation Practice By HS ADAMS Page 2 ... Page 3. **MILK AND FOOD**
SANITATION PRACTICE Page 4. LONDON GEOFFREY CUMBERLEGE OXFORD UNIVERSITY
PRESS Page 5. **MILK AND FOOD SANITATION PRACTICE** ... H~ S;. ADAMS, B.Sc ...

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**Populations of the wood mouse (*Peromyscus leucopus*) subjected
to the applications of DDT and parathion**

WB Jackson - Ecological Monographs, 1952 - Wiley Online Library

... In the case of mammals, it may be passed through the placenta or in the **milk** and affect the young at some stage in their development. Hoffmann & Linduska (1949) have summarized in general terms the effects of **DDT** on various forms of wildlife, and only that portion of the voluminous ...

[Cited by 38 Related articles All 4 versions](#)

[Agranulocytosis occurring after exposure to a **DDT** pyrethrum aerosol bomb](#)

CS Wright, CA Doan, HC Haynie - The American journal of medicine, 1946 - amjmed.com

... The Dispensary of the United States of America. 23rd ed., Philadelphia, 1943. JB Lippincott Co. 37. WOODWARD, G., OFNER, RR and MONTGOMERY, CM Accumulation of **DDT** in the body fat and its appearance in the **milk** of dogs. Science, 102: 177, 1945.

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[\[PDF\] journalofdairyscience.org](#)

[Excretion of heptachlor epoxide in the **milk** of dairy cows fed heptachlor-sprayed forage and technical heptachlor](#)

RE Ely, LA Moore, PE Hubanks, RH Carter... - Journal of Dairy ..., 1955 - Elsevier

... REFERENCES (1) CAKTER, R. IX., AND I-luBANKS, PE Determination of **DDT** Deposits on Fruits, Vegetables and Vegetation. J. Assoc. O-c. Agr ... 1953. (3) DAVIDO'W, B., RADOMSKI, J'. L., AND ELY, RE Excretion of Heptachlor Epoxide in **Milk** of a Dairy Cow Fed Heptachlor ...

[Cited by 29 Related articles All 2 versions](#)

[Purpura following exposure to **DDT**.](#)

FE Karpinski Jr - Journal of Pediatrics, 1950 - cabdirect.org

Five cases of purpura occurring in children following exposure to DDT mixtures are presented. "The known toxic effects of DDT in animals and human beings are briefly discussed. "The purpuric manifestations were extensive and associated with marked thrombocytopenia in four ...

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[Enzymatic Dehydrochlorination of **DDT** by resistant Flies.](#)

J STENBURG, EB Vinson, CW Kearns - Journal of Economic ..., 1953 - cabdirect.org

DDT-resistant house-flies [*Musca domestica* L.] have been shown to dehydrochlorinate DDT to DDE (1, 1-dichloro-2, 2-bis (p-chlorophenyl) ethylene) more rapidly than susceptible ones [RAE, B 38 209; 40 56], and Sternburg & Kearns concluded that the resistance of a strain with which ...

[Cited by 49 Related articles All 3 versions](#)

[DDT residues in soil.](#)

RD Chisholm, L Koblitsky, JE Fahey - Journal of Economic ..., 1950 - cabdirect.org

In cultivated apple orchards sprayed annually for 3 or 4 years, DDT concentrations in the top 3-in. of soil under the trees increased from 17.4 to 79.5 in 3 years and from 14.1 to 60.9 lb./acre in 4 years. DDT contents of 18.0-37.5 lb./acre are reported for peach orchards. The DDT content ...

[Cited by 33 Related articles All 3 versions](#)

[Gesarol" or the new" **DDT**" in the Control of Stable Flies.](#)

R Wiesmann - Soap, 1943 - cabdirect.org

The principal disadvantage of the usual methods of controlling flies in animal sheds in Switzerland is their lack of residual effect. Numerous large scale tests showed that various species of flies are killed in a short time by contact with deposits of Gesarol [a spray concentrate containing ...

[Cited by 3 Related articles All 2 versions](#)

[The Adsorption, Distribution, and Site of Action of **DDT** in **DDT**-resistant and **DDT**-susceptible House Flies using Carbon14 Labelled **DDT**.](#)

EJ LeRoux, FO Morrison - Journal of Economic Entomology, 1954 - cabdirect.org

The technique of experiments in which radioactive (¹⁴C-labelled) DDT was used to study the adsorption, distribution and site of action of DDT in house-flies [*Musca domestica* L.] of a resistant and a susceptible strain [cf. RAE, B 42 139; 43 188] is described, and the results are given ...

[Cited by 36Related articlesAll 3 versions](#)

The detoxification of **DDT** by resistant houseflies and inhibition of this process by piperonyl cyclonene.

AS Perry, WM Hoskins - Science (Washington), 1950 - cabdirect.org

Several investigators have found that the common house-fly, *Musca domestica*, becomes resistant to DDT after one or more seasons' exposure. No marked effect on the action of DDT has been found when synergists are added, such as has been reported with pyrethrins. A study ...

[Cited by 96Related articlesAll 6 versions](#)

Toxaphene, Transmission Studies of **Milk** of Dairy Cows Fed Toxaphene-Treated Hay

GQ Bateman, C Biddulph, JR Harris... - Journal of Agricultural ..., 1953 - ACS Publications

... THE RESIDUE REMAINING On alfalfa hay treated with economic levels of **DDT** and methoxychlor, and the amount of insecticide found in the **milk** and tissues of dairy cows (7, 2), the tissues of lambs (7), and the tissues and eggs of hens (3, 5), after they consumed such treated ...

[Cited by 23Related articles](#)

Effects of oral Dosages of **DDT** on certain Vertebrates.

HS Telford, JE Guthrie - Journal of economic entomology, 1946 - cabdirect.org

DDT administered by stomach tube to goats at 1-5-3-3 gm. per kg. body weight caused mild to severe tremors from which the animals recovered, with the exception of one goat in poor condition at the outset, which became prostrate in 52 hours and was destroyed. A goat that received ...

[Cited by 2Related articlesAll 4 versions](#)

Toxicity of **DDT** to Fish.

JM Ginsburg - Journal of Economic Entomology, 1945 - cabdirect.org

The following is substantially the author's summary. Observations in the course of field experiments in New Jersey with mosquito larvicides containing DDT indicated that this chemical was toxic to three kinds of fish. Laboratory experiments with various concentrations of DDT applied ...

[Cited by 30Related articles](#)

The Absorption, Distribution and Metabolism of **DDT** in **DDT**-resistant Houseflies.

AS Tahori, WM Hoskins - Journal of Economic Entomology, 1953 - cabdirect.org

Previous work has shown that certain strains of DDT-resistant house-flies [*Musca domestica* L.] can change absorbed DDT into the relatively non-toxic DDE [RAE, B 39 211]. However, the fact that apparently healthy DDT-resistant flies can store in their bodies amounts of DDT that ...

[Cited by 57Related articlesAll 4 versions](#)

Development of a Strain of Houseflies Resistant to **DDT**.

AW Lindquist, HG Wilson - Science (Washington), 1948 - cabdirect.org

i. About 300 houseflies from a laboratory colony were exposed to an atomized mist of DDT in kerosene; about 10 per cent, survived and these were used as parents for the next generation. By repeating this for fourteen generations, a markedly DDT-resistant strain was developed ...

[Cited by 41Related articlesAll 6 versions](#)

Rate of Evaporation of **DDT**.

EE Fleck - Journal of Economic Entomology, 1944 - cabdirect.org

To determine the rate at which DDT [2, 2-bis (parachlorophenyl)-1, 1, 1-trichlorethane] will evaporate from a dusted surface, a glass plate 50 sq. cm. in area with a deposit of 63-36 mg. DDT from a 325-mesh sieve was put in an air bath, for which a four-inch tube was used, and air was ...

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The Toxicity of **DDT** to *Daphnia*.

[BG Anderson - Science \(Washington\), 1945 - cabdirect.org](#)

This is a note to the effect that DDT in concentrations of 1 to 100 parts per billion [thousand million] of water immobilizes *Daphnia magna*. Less than 1 part per billion is ineffective. These results may be important in relation to the use of DDT for mosquito control, since in many localities ...

[Cited by 28](#)[Related articles](#)[All 7 versions](#)

ith DDT.

[M Hertig, RA Fisher - Bulletin of the United States Army Medical ..., 1945 - cabdirect.org](#)

Sandflies of the genus *Phlebotomus* are notoriously difficult to control but an observation of their habits suggested that they might be vulnerable to DDT films on the walls of buildings. Those species whose habits have been studied progress by short flights, alighting on stones and ...

[Cited by 31](#)[Related articles](#)[All 2 versions](#)

[\[PDF\] nih.gov](#)

DDT and its application in veterinary medicine

[CR Twinn - Canadian journal of comparative medicine and ..., 1946 - ncbi.nlm.nih.gov](#)

... The transmission of **DDT** through the **milk** of animals has also been demonstrated with rats and goats by Telford and Guthrie (33). Flies A valuable characteristic of **DDT** is its extreme toxicity to flies and mosquitoes even when present in minute quantities ...

[Cited by 4](#)[Related articles](#)[All 3 versions](#)

DDT and related insecticides in milk.

[EF Knipling - Journal of Milk and Food Technology, 1950 - cabdirect.org](#)

A review of recent literature on the occurrence of insecticide residues in milk following the application of DDT and related insecticides to feed crops, to dairy cows and in dairy barns. The insecticides mentioned in particular are DDT ...

[Cited by 2](#)[Related articles](#)

Improved Procedure for Extraction of DDT in Milk

[H Mann, R Carter - Analytical Chemistry, 1951 - ACS Publications](#)

'THE determination of **DDT** in milk by the colorimetric method described by Schechter et al.(4) is a lengthy process; it is advantageous to introduce every time-saving device possible. The procedure heretofore used in this laboratory in carrying out the method has included as the ...

[Cited by 1](#)[Related articles](#)[All 2 versions](#)

DDT Part II. Detection and quantitative determination of DDT (in milk).

[S Krauze, CJ Rzymowska - Roczniki Panstwowe Zakladu Hig., 1950 - cabdirect.org](#)

The authors describe in detail a number of methods used for the detection and quantitative determination of DDT in different products including milk. [See DSA 13 (4) 522 (1951), MANN et al and DAVIDOW; and 9 (1) 67 (1947) CANTER, and SCHECHTER et al.] FL.

[Cited by 1](#)[Related articles](#)

The control of Phlebotomus in Peru with DDT.

[M Hertig, GB Fairchild - American Journal of Tropical Medicine, 1948 - cabdirect.org](#)

The authors, both of whom are authorities on the entomological side of the subject, give an account of the control of *Phlebotomus* in Peru with DDT, together with a number of valuable notes on the biology of these insects. Preliminary work in the Mediterranean had shown that spraying ...

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[\[PDF\] jfoodprotection.org](#)

The influence of DDT wettable powder on the methylene blue reduction test in milk

[SJ Millian, HH Weiser - Journal of Milk and Food Technology, 1953 - jfoodprotection.org](#)

DDT has been detected in the **milk** of cows fed forage crops exposed to the insecticide. **DDT**, in the form of a wettable powder, was added to raw **milk** to determine its effect on the methylene blue reduction test. The results indicate that the presence of appreciable ...

[Cited by 1](#)[Related articles](#)[All 2 versions](#)

[Synergistic Action with **DDT** toward resistant House Flies.](#)

AS Perry, WM Hoskins - *Journal of Economic Entomology*, 1951 - [cabdirect.org](#)

The investigations here recorded, made in California between March 1949 and June 1950, had the object of finding a Synergist that would make **DDT** effective against strains of house-flies (*Musca domestica* L.) that are resistant to it. Acetone solutions of p, p' **DDT** alone and combined ...

[Cited by 59](#)[Related articles](#)[All 3 versions](#)

[Chemoreception in insects and the action of **DDT**](#)

T Smyth Jr, CC Roys - *The Biological Bulletin*, 1955 - [journals.uchicago.edu](#)

... LE Chadwick of the Army Chemical Center, and for **DDT**-sensitive blowflies (*Phormia regina* Meigen) obtained from Professor VG Dethier of the Johns Hopkins University. The larvae were reared on a **milk**-yeast-agar medium at 30°C. Pupae and ...

[Cited by 49](#)[Related articles](#)[All 3 versions](#)

[Laboratory Studies of **DDT**-Resistant House Flies \(Diptera\) in Canada¹](#)

LAO Roadhouse - *The Canadian Entomologist*, 1953 - [cambridge.org](#)

... glass panels were washed and again treated after each exposure so that all flies were exposed to the same residual concentration of **DDT**. As soon as the flies were introduced into the test cage, the machine was turned on and the zero time marked on the tape. **Milk** soaked in a ...

[Cited by 5](#)[Related articles](#)[All 2 versions](#)

[inst Insecticide-resistant House Flies.](#)

RB March, RL Metcalf, LL Lewallen - *Journal of Economic ...*, 1952 - [cabdirect.org](#)

Strains of the house-fly [*Musca domestica* L.] that are not controlled by deposits of the insecticides in general use have developed in many parts of southern California [cf. RAE, B 40 14]. To investigate the possibility of activating the insecticides against the resistant strains, 96 compounds ...

[Cited by 60](#)[Related articles](#)[All 3 versions](#)

[Resistance of Insects to Insecticides: the Metabolism of injected **DDT**.](#)

FH Babers, JJ Pratt Jr - *Journal of Economic Entomology*, 1954 - [cabdirect.org](#)

The following is based on the authors' summary. The ability of a resistant strain of *Musca domestica*, L. to metabolise **DDT** was compared with that of a susceptible strain following the topical application on individual flies or injection into them of measured dosages. Analyses of ...

[Cited by 38](#)[Related articles](#)[All 3 versions](#)

[Effect of Feeding **DDT**-Treated Alfalfa Hay to Swine and of Feeding the Swine Tissues to Rats: Two Figures](#)

LE Harris, JR Harris, FL Mangelson... - *The Journal of ...*, 1953 - [academic.oup.com](#)

... **DDT** accumulated in the fatty tissue and **milk** of dairy cows (Biddulph et al., '50), the fatty tissue and eggs of chickens (Bryson et al., '50) and the fat of lambs (Harris et al., '49) ... L. MADSEN 1950 **DDT** in **milk** and tissues of dairy cows fed **DDT**-dusted alfalfa hay ...

[Cited by 4](#)[Related articles](#)[All 4 versions](#)

[\[PDF\] \[biodiversitylibrary.org\]\(#\)](#)

[\[PDF\] Facts and fallacies about **DDT**](#)

HH Stage - *Mosquito news*, 1946 - [biodiversitylibrary.org](#)

... It has been shown that when **DDT** is ingested by **milk** cows as much as 3 parts of **DDT** per million can be reclaimed from the Page 5 ... Flies and rats have been killed by feeding on **milk** produced by cows fed **DDT**, and nursing pups have been killed by feeding **DDT** to the mothers ...

[Cited by 2](#)[Related articles](#)[All 3 versions](#)

" DDT" Poisoning in Man.

IM Mackerras - Medical Journal of Australia, 1946 - cabdirect.org

The, following observations on DDT poisoning were made in New Guinea: -(1) Poisoning by ingestion. A native cook-boy used DDT in mistake for baking powder to make a tart, which was eaten by some 25 soldiers. All suffered from a feeling of giddiness and weakness, commencing ...

[Cited by 20Related articlesAll 5 versions](#)

Determination of DDT Residues on Corn. Comparison of Analytical Methods

J Fahey, H Rusk - Analytical Chemistry, 1951 - ACS Publications

... When the nitrated solution is diluted with water, samples containing appreciable quantities of **DDT** will be **milk**-. This milkiness can be taken as an indicator of the dilution, or aliquot part, needed for the final color formation ...

[Cited by 4Related articles](#)

DDT Intoxication in a Family of Southern Taiwan.

HC Hsieh - Arch. Indust. Hyg. & Occupational Med., 1954 - cabdirect.org

Observations on accidental DDT intoxication were made in a family eating DDT-contaminated pork dumplings in a rural village of southern Taiwan. "Seven of 11 members of the family, eating approximately 16.3 to 120.5 mg. of pure DDT per kilogram of body weight, showed multiple ...

[Cited by 29Related articlesAll 3 versions](#)

DDT penetration prevented by adding aluminum stearate to DDT-kerosene solutions.

W Ebeling - Journal of economic entomology, 1945 - cabdirect.org

The addition of 1 per cent. aluminum stearate to kerosene greatly retards its penetration into foliage leaves. The effect when a DDT solution in kerosene (4 per cent.) is used, is to keep the solution on the surface of the leaves so that DDT crystals are left exposed instead of penetrating ...

[Cited by 17Related articlesAll 4 versions](#)

Metabolism of chlorinated hydrocarbon insecticides

G Woodard, B Davidow, A Lehman - Industrial & Engineering ..., 1948 - ACS Publications

... amount of **DDT** present in the silage. Table V. **DDT** in **Milk** from Cows Fed Corn Silage Containing 5 10 PPM **DDT** Days on Expt. 31 42 65 85 100 **DDT** in **Milk**, PPM 0.3 0.2 0.3 0.1 0.5 Based on these experiments, feeding corn silage ...

[Cited by 19Related articles](#)

Detoxification of DDT as a Factor in the Resistance of House Flies.

AS Perry, WM Hoskins - Journal of Economic Entomology, 1951 - cabdirect.org

Details are given of a degradation of DDT to the relatively harmless DDE [I, I-dichloro-2, 2-bis(p-chlorophenyl)ethylene] in four strains of house-flies. [Musca domestica L.] of different degrees of resistance [see preceding abstract] treated by topical application of DDT in acetone ...

[Cited by 68Related articlesAll 3 versions](#)

thion by fruits.

GE Carman - Advances Chem. Ser., 1950 - cabdirect.org

Absorption of insecticide residues of DDT and parathion by fruit was investigated. Specific techniques for the physical separation of component fruit parts with minimization of sample contamination are described. The relatively rapid penetration of the toxicants was followed by ...

[Cited by 19Related articles](#)

DDT-Resistant House-Flies.

CM Harrison - Annals of Applied Biology, 1950 - cabdirect.org

The author reports the progress of research in London on two strains of house-fly (Musca domestica) obtained from Italy, (a) from, an area where DDT house-spraying had produced evidence of a resistant strain and (b) from Rome, where virtually no spraying had been done ...

[Cited by 16](#)[Related articles](#)[All 3 versions](#)

Effect of **DDT** ingestion on total cholesterol content of ovaries of white rat.

OE Tauber, AB Hughes - Proceedings of the Society for ..., 1950 - journals.sagepub.com

... Usually 1,0100 g of each level of **DDT** were made as an experimental diet supply and kept in a covered container for 1 day ... t Ingredients, in %: ground yellow 'corn, 63.75 ; soy bean meal, 10.0; wheat middlings, 10.0; linsced oil meal, 8.0; dried skim **milk**, 5.0; alfalfa meal, 2.0 ...

[Cited by 13](#)[Related articles](#)[All 3 versions](#)

House Flies resistant to **DDT** residual Sprays.

GW Barber, JB Schmitt - Bulletin. New Jersey Agricultural ..., 1948 - cabdirect.org

In April 1948, flies were collected from a hotel at Ellenville, New York, where DDT deposits were falling to give adequate control, though they had been used with great success in the two previous years. In the first paper, summarised results are given of numerous experiments made ...

[Cited by 30](#)[Related articles](#)[All 2 versions](#)

The Genetics of Resistance to **DDT** in *Drosophila melanogaster*.

JC King - Journal of Economic Entomology, 1954 - cabdirect.org

The author describes experiments in which lines of *Drosophila melanogaster* Mg. were developed from a laboratory stock and from a batch of wild flies collected in New York in July 1952, ' by exposing the adults to a DDT aerosol for 4, 8, 16, 24 or 32 minutes and breeding from the ...

[Cited by 31](#)[Related articles](#)[All 4 versions](#)

Effect of Cooking on the **DDT** Content of Beef.

RH Carter, PE Hubanks, HD Mann... - Science ..., 1948 - cabdirect.org

One of a herd of cattle that had received DDT in clover hay from 5th January to 1st April was slaughtered on 10th May, and the carcass was kept in cold ' storage until December. Beef from it was then cooked by five methods or left uncooked and tested for DDT content. Chemical analysis ...

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Excretion of dieldrin in the **milk** of cows fed dieldrin-sprayed forage and technical dieldrin

RE Ely, LA Moore, RH Carter, PE Hubanks... - Journal of Dairy ..., 1954 - Elsevier

... Biol. Med., 79: 236. 1952. (3) CARTER, RH, AND HYBANKS, PE Determination oe **DDT** Deposits oil Fruits, Vege- tables, and Vegetation. J. Assoc. O]jic. .4gr ... t~.;52. (9) SAOEI~ O. S., AND SANDERS, (}. P. A BDI Detergent Test for Butterfat in **Milk** and Oilier l)siry Products. Proc ...

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Susceptibility of **DDT**-resistant Houseflies to Other Insecticidal Sprays.

HG Wilson, JB Gahan - Science (Washington), 1948 - cabdirect.org

ii. Flies were exposed to atomized mists of various insecticides in a 100 cu. ft. cabinet. The insecticides were applied at various concentrations and their toxic effects were determined on the normal laboratory fly stock and the strain selected for resistance to DDT as described above ...

[Cited by 23](#)[Related articles](#)[All 6 versions](#)

Failure of **DDT** to control House Flies.

WV King, JB Gahan - Journal of economic entomology, 1949 - cabdirect.org

A few reports were received in 1947 and many in 1948 of the failure of DDT deposits to control *Musca domestica*, L., in the United States under conditions in which similar deposits had formerly proved highly successful. Preliminary tests with flies from various localities near Orlando ...

[Cited by 28](#)[Related articles](#)[All 6 versions](#)

Metabolic Fate of **DDT** when applied to certain naturally tolerant Insects.

J Sternburg, CW Kearns - Journal of Economic Entomology, 1952 - cabdirect.org

It is shown by the experiments described in the first paper, which are noticed in more detail elsewhere [RAE, A 40 347], that *Melanoplus differentialis* (Thos.), *M. femur-rubrum* (Deg.) and larvae of *Epilachna varivestis* Muls, and *Eulia* (*Argyrotaenia*) *velutinana* (Wlk.) can all degrade ...

[Cited by 55](#)[Related articles](#)[All 2 versions](#)

n of DDT by resistant Cockroaches.

FH Babers, CC EOAN - *Journal of Economic Entomology*, 1954 - [cabdirect.org](#)

Experiments were carried out to determine whether cockroaches (*Blattella germanica* (L.)) of a Texas strain highly resistant to chlordane and somewhat so to certain other insecticides [RAE, B 41 179; 42 136] could dehydro-chlorinate DDT faster than a susceptible strain. The stock ...

[Cited by 18](#)[Related articles](#)[All 2 versions](#)

Pathologic action of DDT and certain of its analogs and derivatives.

RD Lillie, MI Smith, EF Stohlman - *Arch. Pathol.*, 1947 - [cabdirect.org](#)

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DDT Resistance in an Italian Strain of *Musca domestica* L.

CM Harrison - *Bulletin of Entomological Research*, 1952 - [cambridge.org](#)

... cube cages, and on emergence flies were fed with sugar and a solution of 50 per cent, **milk** and 50 per cent, water ... Preliminary tests in which flies of the Roma strain were exposed to filter papers impregnated with **DDT** gave the following information :— (1) Male flies were more ...

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Thermal Decomposition of DDT and Benzène Hexaehloride

Mixtures.

FA Gunther - *Journal of economic entomology*, 1947 - [cabdirect.org](#)

" Thus it becomes apparent that benzene hexachloride in any of the forms studied has a pronounced deleterious effect upon the thermal stability of DDT in admixture. In all probability the hexachloride preparations contained minute traces of iron or other catalyzing materials which ...

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DDT-resistant House Flies and Mosquitoes.

WV King - *Journal of Economic Entomology*, 1950 - [cabdirect.org](#)

The following is mainly based on the author's summary. Tests were carried out in dairy barns in two localities in Florida in 1949 to determine the relative effectiveness of different insecticides applied as treatments to leave a toxic residue against house-flies (*Musca domestica* L.) that ...

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The Distribution of Radioactive DDT in House Flies.

AW Lindquist, AR Roth, RA Hoffman... - *Journal of Economic ...*, 1951 - [cabdirect.org](#)

" The distribution of radioactive DDT in various internal organs and external parts of resistant house flies, *Musca domestica* L., was studied. Flies topically treated with 8 to 11.25 micrograms of DDT each showed from 26 to 34 per cent of the total absorbed in the internal organs and ...

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Effect of Temperatures on Knockdown and Kill of Houseflies exposed to DDT.

AW Lindquist, HG Wilson, HO Schroeder... - *Journal of Economic ...*, 1945 - [cabdirect.org](#)

Temperature exerts a marked effect on the rate of knock-down and the final mortality of flies exposed to treated surfaces. When exposed at a temperature of 70°F. and transferred after being knocked down to a temperature of 80°F. to 100°F. they recover, collapsing again when put ...

[Cited by 41](#)[Related articles](#)[All 3 versions](#)

Insecticidal Activity of some Alkoxy Analogs of DDT.

EA Prill, A Hartzell, JM Arthur - *Science* (Washington), 1945 - [cabdirect.org](#)

In comparative tests of 2, 2-bis (parachlorophenyl)-1, 1, 1-trichlorethane (DDT) and several synthetic alkoxy analogues of it against *Musca domestica* by the Peet-Grady method, a solution of 2.5 gm. DDT per litre of a refined petroleum distillate gave 42 per cent, knock-down in ten minutes ...

[Cited by 23](#)[Related articles](#)[All 7 versions](#)

The potentiation of **DDT** against resistant houseflies by several structurally related compounds.

WT Sumerford, MB GUETTE, KD Quarterman... - Science ..., 1951 - cabdirect.org

Recently there have been a series of reports of substances acting as synergists with DDT against DDT-resistant house-flies. The authors describe investigations on DDT analogues as synergists. Of eleven analogues tested 1, 1-bis(p-chlorophenyl)-ethanol (DMC) was outstanding ...

[Cited by 28](#)[Related articles](#)[All 6 versions](#)

The new insecticidal material **DDT**

IM Heilbron - Journal of the Royal Society of Arts, 1945 - JSTOR

... It has been reported from the USA, for instance, that the application of **DDT** sprays to the walls of cattle-sheds badly infested with flies, caused a rapid drop in the fly population, coupled with a more satisfied condition of the animals resulting in higher **milk** yields ...

[Cited by 4](#)[Related articles](#)[All 2 versions](#)on. Report of a Fatal Case.

K Biden-Steele, RE Stuckey - Lancet, 1946 - cabdirect.org

A labourer swallowed in its concentrated form with fatal-results 6 oz. of DDT emulsion intended to be diluted 40 times. " The necropsy showed pulmonary and gastrointestinal congestion.

[Cited by 16](#)[Related articles](#)[All 5 versions](#)

Airplane Application of **DDT** Larvicides.

CC Deonier, RW Burrell - Journal of Economic Entomology, 1945 - cabdirect.org

The application of DDT as a dust from aircraft presents several technical difficulties, and is not a certain means of killing mosquito larvae. The application of solutions, or emulsions, by this means, however, is a very promising method of mosquito control. Less weight of material need ...

[Cited by 11](#)[Related articles](#)[All 3 versions](#)

Inhibition of the catalyzed thermal decomposition of **DDT**.

FA Gunther, LR Tow - Science (Washington), 1946 - cabdirect.org

The presence of iron catalyses the decomposition (dehydrohalogenation) of DDT at high temperatures, and this may be responsible for much of the loss of active DDT from thermally generated smokes, etc., and possibly also from residual deposits exposed to weathering. Two ...

[Cited by 12](#)[Related articles](#)[All 8 versions](#)

Toxicity of Dichloro-Diphenyl-Trichlorethane (**DDT**) to Goldfish and Frogs.

MM Ellis, BA Westfall, MD Ellis - Science (Washington), 1944 - cabdirect.org

Goldfish and frogs are more susceptible to DDT than rats, cats and rabbits. Single doses of 63-200 mgm. per kgm. were lethal when dissolved in olive oil and incorporated in food pellets which were swallowed by gold fish weighing 6-10 gm. In this range the mortality was 55 per cent ...

[Cited by 25](#)[Related articles](#)[All 6 versions](#)

Contact Dermatitis due to **DDT**. Report of a Case.

ML Niedelman - Occupational medicine, 1946 - cabdirect.org

A case of contact dermatitis due to DDT is presented. It is presumed that the kerosene was not the primary contactant. Physicians should be on the alert for this type of dermatitis.

[Cited by 13](#)[Related articles](#)[All 3 versions](#)

An increase in the duration of the life cycle of **DDT**-resistant strains of the house fly.

D Pimentel, JE Dewey, HH Schwardt - Journal of Economic ..., 1951 - cabdirect.org

Few careful observations of the length of life cycle of DDT-resistant and susceptible flies have been made. The length of life cycle of 5 strains of houseflies, one susceptible, one highly DDT-resistant, and 3 with intermediate resistance were compared in the laboratory. The egg ...

[Cited by 52](#)[Related articles](#)[All 3 versions](#)

The toxic effects of prolonged ingestion of **DDT** on dogs with special reference to lesions in the brain.

W Haymaker, AM Ginzler, RL Ferguson - American Journal of ..., 1946 - cabdirect.org

From clinical observations as well as physiologic and electroencephalographic data, it appears that the cerebellum is the chief portion of the nervous system on which DDT acts. The same would seem to hold pathologically, inasmuch as degenerative changes in DDT-intoxicated ...

[Cited by 59](#)[Related articles](#)[All 3 versions](#)

A Comparison of **DDT**-resistant and non-resistant House Flies.

RB March, LL Lewallen - Journal of Economic Entomology, 1950 - cabdirect.org

Wiesmann reported morphological and physiological differences between a DDT-resistant strain of house-flies [*Musca domestica* L.] from Sweden and a non-resistant strain from Switzerland [RAE, B 37 217]. A study was therefore undertaken to determine whether similar differences ...

[Cited by 28](#)[Related articles](#)[All 2 versions](#)

The toxicity of **DDT** to certain forms of aquatic life.

PM Eide, CC Deonier, RW Burrell - Journal of Economic ..., 1945 - cabdirect.org

The following is the authors' summary. DDT in concentrations greater than 0.1 part per million was found to be toxic to goldfish in laboratory tests. In field tests, surface applications of DDT as a dust and in oils were not harmful to fish in dosages used for mosquito control. Other cold ...

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Mode of Action of Pesticides, Absorption and Excretion, Distribution, and Metabolism of Carbon-14-Labeled **DDT** by the American Cockroach

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October 11, 2019

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1. REQUESTED REVIEWS AND CHARGE QUESTIONS

For this litigation, I have been asked to do the following or answer the following questions;

1. Did the scientific methods and procedures used in ATSDR/WDOH health advisories follow generally accepted and standard scientific practice in calculating health risks from eating PCB-contaminated fish?
2. Are current fish advisories issued by the WDOH to warn the public of the health threats posed by eating PCB-contaminated fish from the Spokane River scientifically tenable?
3. Do the PCB fish concentrations currently limit the number of fish recreational fishermen should eat based on concerns regarding unacceptable systemic toxic effects and cancer?
4. Have the City of Spokane's past efforts to reduce the PCB loading into the Spokane River resulted in reducing PCB contamination of fish tissue and reduced health threats?

2. SUMMARY OPINIONS

1. The State of Washington has issued Fish Consumption Advisories based on PCBs for the following fish in the following reaches of the Spokane River:
 - Little Falls Pool – Little Falls Dam to Long Lake Dam:
 - Largescale Sucker – Up to 4 meals per month
 - Northern Pikeminnow – Up to 4 meals per month
 - Long Lake (Lake Spokane):
 - Brown Trout – Up to 1 meal per month
 - Common Carp – 0 meals per month
 - Largescale Sucker – Up to 1 meal per month
 - Mountain Whitefish – Up to 2 meals per month
 - Spokane Arm – Mouth upriver to Little Falls Dam
 - Brown Trout – Up to 4 meals per month
 - Largescale Sucker – Up to 1 meal per month
 - Rainbow Trout – Up to 4 meals per month
 - Upriver Dam to Nine Mile Dam
 - Largescale Sucker – Up to 2 meals per month

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- Mountain Whitefish – Up to 1 meal per month
 - Rainbow trout – Up to 2 meals per month
2. The current fish advisories issued by the WDOH are scientifically tenable and are necessary to protect Washington state residents.
 3. The ATSDR/WDOH Health Consultation's recommendations, if followed, will reduce the health threat posed by eating PCB-contaminated fish while maximizing the greatest number of fish meals that can be consumed without fear of PCB-induced toxic effects.
 4. The risk assessment presented in the latest 2011 WDOH Health Consultation shows that PCBs pose a cumulative lifetime cancer risk of 1.1E-4 (one-in-ten-thousand). This risk levels far exceeds the *de minimis* acceptable risk level by 100-fold and to reach acceptable risk levels the fish tissue levels must be reduced by 100-fold.
 5. Studies have shown that the groups of people most at risk from eating PCB-contaminated Spokane River fish are from low-income environments.
 6. While PCBs were banned decades ago they are still detected in most American bodies today and the highest PCB body burdens in the general public have been shown to be those that eat a diet rich in fish tissue. Sport fishermen have been shown to have body burdens 2-3 times the levels of non-fish eating people.
 7. Spokane has taken action to prevent PCB loading to the Spokane river to improve water quality, reduce fish PCB-contaminant levels, lower the body burden levels in people that eat Spokane fish. This effort will have a significant impact on lowering PCB body burden and the risk of PCB-related cancer and non-cancer disease.
 8. From between 2012 and 2018, Spokane's remedial activities reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 1.4-3.1%.
 9. From between the 2001-2005 period and 2030, Spokane's remedial activities will have reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 11-17%.

This assumes that Spokane performs the future remedial activities discussed in Michael Baker International's expert report.

10. From between 2012 and 2030, Spokane's remedial activities will have reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 5.5-9%. This assumes that Spokane performs the future remedial activities discussed in Michael Baker International's expert report. This represents a significant reduction in PCB body burden over just an 18-year period and Spokane's efforts will have the greatest impact on reducing PCB exposures.

3. INTRODUCTION

Polychlorinated biphenyls (PCBs) have been detected at high levels throughout the entire length of the Spokane River since samples were first collected and analyses conducted for this complex group of persistent, bioaccumulative, and toxic group of contaminants (PBTC). PCBs have been detected at elevated levels in Spokane River water, sediments, fish, and effluents being discharged into the river. The Washington Department of Ecology (WDOE) first confirmed as early as the 1980s (WDOE 2011: Hopkins et al., 1985) that PCB contamination of fish caught in the Spokane River and subsequently eaten by recreational fishermen were contaminated with very high concentrations of PCBs, which followed the U.S. Environmental Protection Agency (U.S. EPA) ban of PCBs in 1977. Since that time, numerous investigations have documented the extent of river contamination by PCBs and determined the fish tissue concentrations for impacted segments of the Spokane River. The ultimate purpose of these investigations was to evaluate both the spatial and temporal trends of PCB contamination in different parts of the Spokane River fish and to warn the public of the health threats posed by PCBs as a result of eating different species of PCB-contaminated fish. These public warning were issued in the form of "fish consumption advisories" in which the maximum numbers of fish meals that could be eaten without consumers suffering serious toxic effects (including cancer) were widely communicated to the public (The Washington Department of Health [WDOH] makes these advisories available online. The numbers of fish meals that could be "safely" eaten without harm were based on standard risk assessment procedures that were first developed by U.S. EPA in 2000 and have been adopted by all 50 states; these procedures provide consistency and represent the generally accepted practice in fields of toxicology and risk assessment. The calculated risks were converted into the advisories that remain in place today. The risk assessments that formed the basis for the fish advisories were conducted as a collaborative effort by the Agency for Toxic Substances and Disease Registry [ATSDR] and the WDOH).

While contaminants other than PCB have recently been detected in fish tissue, the fish advisories are still largely based on the high levels of PCB contamination in edible fish. As PCB is the most important and health-threatening industrial chemical contaminant in the Spokane River, any action to reduce PCB loading in the river will ultimately protect public health associated with eating PCB-contaminated fish. Although the U.S. EPA banned Monsanto in 1977 from manufacturing PCBs, Spokane River fish continue to exhibit unacceptably high levels of this group of highly persistent compounds. Because PCBs degrade so slowly in the environment, the Spokane fish will continue to be highly contaminated for many *decades* to come.

It should be stressed that the health risks associated with the PCB-contaminated Spokane River fish are multifaceted and can impact numerous groups of Washington residents. While I have been asked to form an opinion regarding the toxic effects of eating PCB-contaminated fish based on my toxicological expertise, there are issues that need to be discussed because there are indirect and other related issues that must also be considered. Over the last 10–15 years, I have served as an expert in many litigation cases for the U.S. Department of Justice (U.S. DOJ) and have been asked to evaluate the constellation of public health issues surrounding the effects of PCB contamination of polluted rivers—in addition to calculating the risk and providing technical support for fish advisories. What is frequently ignored is that the threat to public health can be direct or indirect. Many groups in a community are impacted by PCB-contaminated rivers, and PCBs can have unintended consequences—even when PCB-contaminated fish are not eaten. Based on my experience, I have identified the following subpopulations of state residents whose health may be impacted:

- Recreational fishermen who follow the ATSDR/WDOH fish advisory recommendations and limit the number of fish they can eat because they are deprived of a state natural resource and cannot enjoy the (inexpensive) health benefits of eating the recommended two fish meals per week of Spokane River fish;
- Low income recreational fishermen and their families who may know the fish are contaminated and must find alternate inexpensive means to supplement their diets;
- Recreational fishermen who know the fish are contaminated but are ignorant of, or disregard, the state fishing advisories and consume PCB-contaminated fish in excess of the fish consumption advisories; and
- Recreational fishermen who are frightened after reading news articles about limits and become scared and overly cautious of eating any caught fish, depriving them of the benefits of eating even the recommended amounts.

Finally, it should be noted that almost all U.S. citizens currently have PCBs in their bodies—and some still have high levels. However, risk assessments (including those presented in the health advisories) do not take into account the PCB body burden that is already elevated in Washington state residents even before they start consuming PCB-contaminated fish. Therefore, risk assessments that focus on fish consumption start with the assumption that the body burden is zero and that PCB exposures start when PCB-contaminated fish are first eaten. In reality, any additional PCB exposures from eating PCB-contaminated fish from the Spokane River will *add* to the background exposures and increase the body burden that has been established for the general population. That is, recreational fishermen who eat PCB-contaminated fish from the Spokane River are also exposed to background PCB levels which everyone in the general US population continues to be exposed to plus the additional PCBs from PCB-contaminated fish.

The bi-yearly Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Surveys show that, although the PCB body burden levels in the population have generally been decreasing, some individuals still have high PCB body burdens.¹ Among this group of persons with high PCB blood levels are those who eat a diet rich in fish tissue. That is, there is a strong association between eating many fish meals and PCB blood levels, particularly among younger groups of people.

4. PRIMARY RELIANCE MATERIALS

1. **1999:** Maret R and Dutton D. Summary of Information on Synthetic Organic Compounds and Trace Elements in Tissue of Aquatic Biota, Clark Fork-Pend Oreille and Spokane River Basins, Montana, Idaho, and Washington, 1974–96. Water-Resources Investigations Report 98-4254. National Water-Quality Assessment Program. 1999.²
2. **1999:** PCBs in Tissue of Fish from the Spokane River, Washington. U.S. Geological Survey prepared in cooperation with the Washington State Department of Ecology. USGS Fact Sheet FS-067-01, U.S. Geological Survey August 2001 (available at <https://pubs.usgs.gov/fs/2001/0067/report.pdf>).³
3. **2005:** Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴
4. **2007:** Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry.

Health Consultation. Evaluation of PCBs, PBDEs and Selected Metals in the Spokane River, Including Long Lake Spokane, Washington. August 28, 2007.⁵

5. **2011:** Serdar D, Lubliner B, Johnson A, Norton D. Toxics Studies Unit, Environmental Assessment Program, Washington State Department of Ecology. Spokane River PCB Source Assessment 2003–2007. April 2011. Publication No. 11-03-013D.⁶
6. **2011:** Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Consultation: Potential Cumulative Health Effects Associated with Eating Spokane River Fish Spokane, Spokane County, Washington. DOH 334-275. August 2011.⁷
7. **2000:** U.S. Environmental Protection Agency. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories - Volume 1, Fish Sampling and Analysis, Third Edition. EPA 823-B-00-007. 2000.⁸

5. OVERVIEW: SPOKANE RIVER PCB CONTAMINANT ASSESSMENT AND FISH TISSUE LEVELS

It has been well-established that the continuous release of PCBs into the Spokane River has resulted in significant bioaccumulation into edible fish tissue and pose a danger to human health for fishermen and their families who have eaten fish in the past and will eat them in the future. One of the most complete studies describing the releases of PCBs into the river and the resulting levels of PCB contamination in all Spokane River environmental media—including fish—is the 2011 WDOE document, *Spokane River PCB Source Assessment 2003–2007*.⁶ As this document states, fish were found to be highly contaminated with PCBs starting with the first studies completed in the early 1980s. These studies showed that many different fish species caught in many sections of the Spokane River had high levels of PCBs from the start of the fish tissue surveys:

PCBs were first analyzed in the Spokane River during Ecology statewide screening-level surveys of contaminants in fish from rivers and lakes (Hopkins et al., 1985; Hopkins, 1991; Serdar et al., 1994). Spokane River fish almost always had high PCB concentrations. For instance, total PCBs in whole fish ranged up to 2,300 ng/g (parts per billion) in northern pikeminnow (Ptychocheilus oregonensis) collected in 1983. Fillets from mountain whitefish (Prosopium williamsoni) and bridgelip sucker (Catostomus columbianus) from Riverside State Park in the City of Spokane were also elevated with total PCB concentrations of 230 and 370 ng/g, respectively. Largescale suckers

(Catostomus macrocheilus) sampled from Lake Spokane had a whole body concentration of 720 ng/g.

The WDOH 2011 assessment was based on a recent fish sampling data set that was accumulated over many different sampling events during the 2003–2007 period. The goal of the PCB assessment study was to quantify PCB contamination in the Spokane River for the purpose of supporting mitigation actions that the State concluded were necessary to protect the public health of Washington residents. To meet specific water quality criteria required by the U.S. EPA, WDOE “analyzed PCBs in river water, industrial and municipal effluents, stormwater, suspended particulate matter, bottom sediments, sediment cores, and fish tissue,” focusing on three major areas of research. Since 1999, surveys in the Spokane River have verified previous data or further characterized the contamination so that its implications are better understood. The three major areas where study efforts have concentrated in the past decade are as follows:

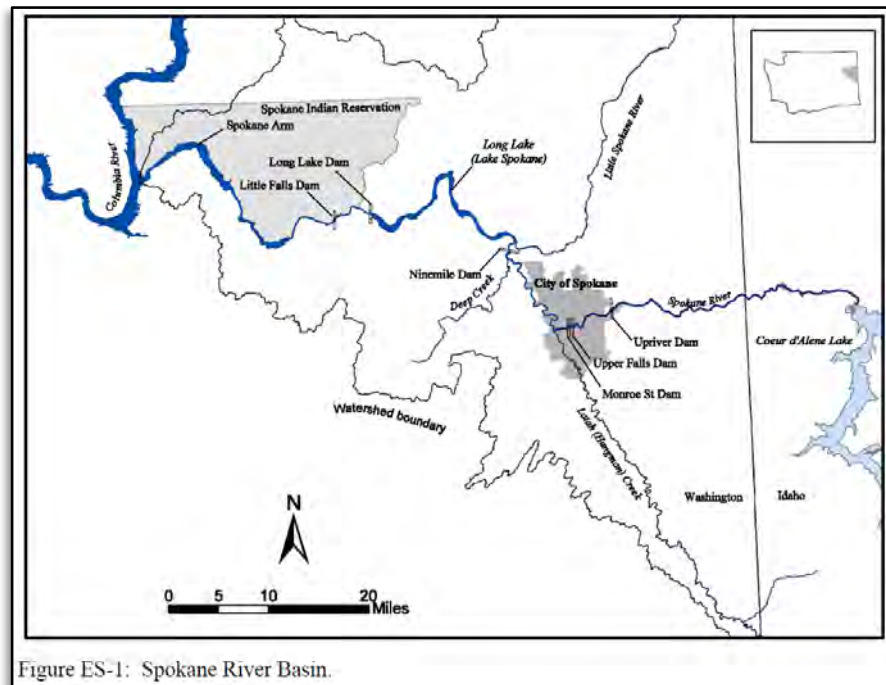
- Continued sampling of fish to evaluate temporal trends and conduct human health risk assessment.
- Continued monitoring of known PCB sources.
- Characterization of the Upriver Dam cleanup site.

I have relied on much of the same data collected by WDOE for this report to evaluate risks and health hazards resulting from consuming the edible PCB-contaminated fish tissue.

5.1. Overview of the Spokane River Basin

WDOE has determined that the Spokane River watershed encompasses over 6,000 square miles in Washington and Idaho. The Spokane River, shown in 0, starts as an outlet of Lake Coeur d’Alene in Idaho and flows west 112 miles to the Columbia River (Lake Roosevelt).

Exhibit 1. Spokane River Watershed



Source: Serdar D, Lubliner B, Johnson A, Norton D. Toxics Studies Unit, Environmental Assessment Program, Washington State Department of Ecology. *Spokane River PCB Source Assessment 2003–2007*. Publication No. 11-03-013D. April 2011.⁶

The study area covered the Spokane River from the Idaho border to the Columbia River, and researchers found that PCB concentrations increased downstream and that most concentrations exceeded the WDOH fish consumption criteria of 5.3 ng/g (ppb):

Total PCB concentrations in water increased with successive reaches moving downstream from the Idaho border (106 pg/l, parts per quadrillion) to lower Lake Spokane (formerly Long Lake; 399 pg/l), with a corresponding eight-fold increase in loads (477–3,664 mg/day), on average. The Washington State PCB human health criterion for surface water is 170 pg/l. Although PCB concentrations in Spokane River fish are generally much lower than historical levels, fish in most areas did not meet the state's human health criterion in edible tissue (5.3 ng/g, parts per billion).

In addition to finding that most edible fish tissue in the WDOE database had PCB levels that exceeded the State's criterion, Serdar et al. also concluded that the levels far exceeded the Spokane Tribe criterion, which is more than 50 times more restrictive than that of the State:

A PCB loading scenario was proposed to meet the Spokane Tribe human health water quality criterion for total PCBs (3.37 pg/l, equivalent to 0.1 ng/g in tissue). The scenario requires a 95% PCB load reduction at the Idaho border, a 97% load reduction in the Little Spokane River, and $\geq 99\%$ reductions in municipal, industrial, and stormwater discharges. A food web bioaccumulation model indicated that PCB loads in water and PCB concentrations in sediment would require large reductions to meet the Spokane Tribe criterion.

WDOE (2011) compares different acceptable fish tissue levels (ng/g: ppb) of PCBs to protect human health that are directly correlated with the different assumptions about the fish tissue consumption rates (kg/day).

Exhibit 2. Table 3 from WDOE 2011

Table 3. Water and Fish Tissue Criteria or Thresholds for Total PCBs ^a (pg/l: picograms per liter; parts per quadrillion; ng/g: nanograms per gram; parts per billion).

Regulation or Guidance	Aquatic Life - Water		Human Health ^{bc}		Fish Tissue Consumption Rate (kg/day)
	(chronic) (pg/l)	(acute) (pg/l)	Water (pg/l)	Tissue (ng/g)	
National Toxics Rule (40 CFR 131)	--	--	170	5.3	0.0065
Washington Water Quality Standards (Ch. 173-201A WAC)	1.4 x 10 ^{4(d)}	2 x 10 ^{6(d)}	--	--	--
Spokane Tribe Water Quality Standards (Resolution 2003-259)	1.4 x 10 ^{4(e)}	2 x 10 ^{6(f)}	3.37	0.1	0.0863
EPA National Recommended Water Quality Criteria (EPA, 2002)	--	--	64	2.0	0.0175
EPA Screening Value for Recreational Fishers (EPA, 2000a)	--	--	--	2.0	0.0175
EPA Screening Value for Subsistence Fishers (EPA, 2000a)	--	--	--	0.245	0.142

^a total PCBs (sum of detected Aroclors, homologue groups, or congeners).

^b based on a one-in-a-million (10⁻⁶) excess lifetime cancer risk.

^c for consumption of organisms and water.

^d 24-hr average not to be exceeded.

^e A one-hour average not to be exceeded more than once every three years on average.

^f A four-day average not to be exceeded more than once every three years on average.

Source: Serdar D, Lubliner B, Johnson A, Norton D. Toxics Studies Unit, Environmental Assessment Program, Washington State Department of Ecology. *Spokane River PCB Source Assessment 2003–2007*. Publication No. 11-03-013D. April 2011.⁶

WDOE (2009) described how it calculated the freshwater criterion of 5.3 ng/g for human consumption of fish tissue for the National Toxics Rule (NTR) and that it was based on the *de minimis* risk cancer level of 1E-6 and a PCB bioconcentration factor of 31,200 L/kg.⁹

Exhibit 3. Human Health Criteria Equation from WDOE 2011

Equation 1.
$$HHC = \frac{RF \times BW \times (10^9 \text{ pg/mg})}{q1^* \times [WC + (FC \times BCF)]}$$

Where:

- HHC = human health criteria.
- RF (risk factor) = the acceptable level of cancer risk. Washington's acceptable upper-bound excess cancer risk is one in a million (10^{-6}) for a lifetime exposure.
- BW (body weight) = the average body weight of the consumer. The NTR uses an average consumer body weight of 70 kg.
- q1* (cancer slope factor) = the cancer potency of each chemical. The NTR uses a q1* of 2 per mg/kg-day for PCBs.
- WC (water consumption) = the average daily consumption of water by a consumer. The NTR uses a water consumption rate of 2 L/day.
- FC (fish consumption) = the average fish tissue consumption by a consumer. The NTR uses a fish tissue consumption rate of 0.0065 kg/day.
- BCF (bioconcentration factor) = the concentration of a chemical in tissue accumulated through gill and skin divided by the concentration in the water column. The NTR uses a BCF of 31,200 L/kg for PCBs.

The water quality criterion can be converted to an equivalent fish tissue criterion using the BCF in Equation 2, where C_w is the concentration in water and C_t is the concentration in tissue:

Equation 2.
$$BCF = \frac{C_t}{C_w}$$

Source: Serdar D, Lubliner B, Johnson A, Norton D. Toxics Studies Unit, Environmental Assessment Program, Washington State Department of Ecology. *Spokane River PCB Source Assessment 2003–2007*. Publication No. 11-03-013D. April 2011.⁶

Based on the above information—which is set at the *de minimis* carcinogenic of one-in-one million excess lifetime cancers—the NTR-equivalent fish tissue concentrations of PCBs in edible tissue (C_t) is 5.3 ng/g (ppb; i.e., the “safe” fish tissue PCB concentration). It should be noted, however, that the Spokane Tribe Indian Nation, while also setting its nation-specific acceptable risk to *de minimis* levels, used slightly different exposure assumptions for fish ingestion (approximately 86 gm/day) and the older U.S. EPA carcinogenic slope factor (CSF) of 7.7 mg/kg-day (compared with the current CSF of 2 mg/kg-day) to derive a safe dose or criterion of 0.1 ng/g PCB in edible fish tissue.

The Spokane Tribal narrative section for toxic pollutant standards is nearly identical to that of the State of Washington, including the adoption of a 1E-6 risk level for carcinogens. However, the Tribal numeric human health criteria are substantially lower (more restrictive) than those issued to Washington in the NTR (3.37 vs. 170 pg/L) due to different values used to derive the human health criteria. Tribal standards

employ an aquatic organism consumption rate of 0.0863 kg/day, as opposed to the 0.0065 kg/day fish consumption rate specified in the NTR. In addition, the Spokane Tribe PCB criteria include an older cancer slope factor of 7.7 per mg/kg-d. Using the same approach to derive an NTR-equivalent tissue value as described above in Equation 2 seen in Exhibit 3, the Spokane Tribe human health criteria of 3.37 pg/L translates to an equivalent edible tissue concentration of 0.1 ng/g.

Exhibit 4. Table 5 from WDOH 2011

Table 5. Summary of Total PCB Concentrations in Fish Tissue from the Spokane River (mean concentrations in ng/g, ww).						
Location and Tissue Type	Total PCB Concentrations Measured by:					
	Aroclor Analysis					Congener Analysis
	1993 ^a	1994 ^b	1996 ^c	1999 ^d	2001 ^e	2005 ^f
Rainbow trout - fillet						
State line	--	--	--	106	--	55
Plante Ferry	918	424	799	891	--	153
Above Monroe Dam*	--	145	76	226	--	73
Ninemile	490	371	76	143	--	--
Mountain whitefish - fillet						
Above Monroe Dam	--	568	381	339	--	234
Ninemile	522	139	444	632	--	139
Little Spokane	--	222	145	--	--	--
Upper Lake Spokane	--	--	--	--	73	43
Lower Lake Spokane	780	113	--	--	--	76
Largescale suckers - whole						
State line	--	--	--	120	--	56
Plante Ferry	2,005	531	530	283	--	122
Above Monroe Dam	--	201	116	445	--	1,823
Ninemile	1,210	--	345	680	--	--
Little Spokane	--	440	366	--	--	--
Upper Lake Spokane	--	--	--	--	265	327
Lower Lake Spokane	410	820	--	--	357	254
--no data						
^a Johnson et al., 1994						
^b Ecology, 1995						
^c Johnson, 1997						
^d Johnson, 2000						
^e Jack and Roose, 2002						
^f Serdar and Johnson, 2006						
*Same reach as Mission Park						

Source: Serdar D, Lubliner B, Johnson A, Norton D. Toxics Studies Unit, Environmental Assessment Program, Washington State Department of Ecology. *Spokane River PCB Source Assessment 2003–2007*. Publication No. 11-03-013D. April 2011.⁶

Serdar et al. Future projections of PCB concentrations indicate that the levels in sediments will only decrease by one-half for each decade but note that the primary source of PCB loading into the Spokane River in the upper Lake Spokane is PCB-contaminated stormwater and that “significant” reductions in

water and sediments would be required to reduce fish tissue concentrations at the Spokane Indian Reservation:

Analysis of sediment cores suggests that PCB concentrations at the sediment surface will decrease by one-half approximately every ten years in upper Lake Spokane, although patterns of material deposition upstream of Lake Spokane require further evaluation. Lower Lake Spokane may be the ultimate sink for fine sediments. In lower Lake Spokane, PCBs have decreased by one-half over two decades after steep declines during the 1960s to mid-1980s... Current PCB concentrations in fish tissue are lower than they have been historically. This may be due in part to natural attenuation and significant reductions in point-source PCB contributions over the past 10 to 15 years. The lack of decline in PCB levels in fish from the Mission Park reach of the river supports the conclusion about the importance of stormwater as a PCB source. A food web bioaccumulation model was used to predict PCB concentrations in fish tissue from PCB levels in water and sediments. This model indicates that significant reductions in sediment PCB concentrations would be required to reduce fish tissue to a Spokane Tribe target concentrations at their reservation.

If the State's biodegradation model is correct—that it will take 10 years to reduce the *surface* PCB concentrations by one-half—it means that it will take a century to reduce the concentrations to zero under current conditions, because it takes 10 half-lives to reduce the concentration to zero.

It should be noted that even if there is a reduction in PCBs in the sediments by one-half each decade, WDOE does not take into account that there is a very slow elimination rate from the human body once PCB-contaminated fish are eaten. When PCBs are ingested by anglers and their families, they will (again) take 10 half-lives for PCBs to be completely eliminated from those eating the PCB-contaminated fish. For example, Aroclor 1254, which has a half-life elimination rate from the human body of 4.8 years¹⁰ would only be totally eliminated (assuming exposure stopped) after 48 years for a person consuming a fish meal today. Obviously, with each passing year of continuously eating PCB-contaminated fish from the Spokane River, eliminating PCBs from Washington state residents will significantly (decades) lag behind the PCB reduction assumed from river sediments.

6. FISH CONSUMPTION ADVISORIES FOR THE SPOKANE RIVER

WDOE first documented PCB contamination in Spokane River fish in the early 1980s (Hopkins et al. 1985).¹¹ Fish tissues from different species have continued to be measured for PCB levels in edible tissue to the present day at different segments of the Spokane River. This section presents a summary of the ATSDR/WDOH (ATSDR 2005, 2007, and 2011) Health Consultations in which fish consumption advisories were derived.^{4,5,7} My review of those documents revealed that the recommended number of fish meals ATSDR/WDOH calculated for different fish species were well-supported by the best available fish tissue PCB data and toxicological/risk assessment methods and protocols.

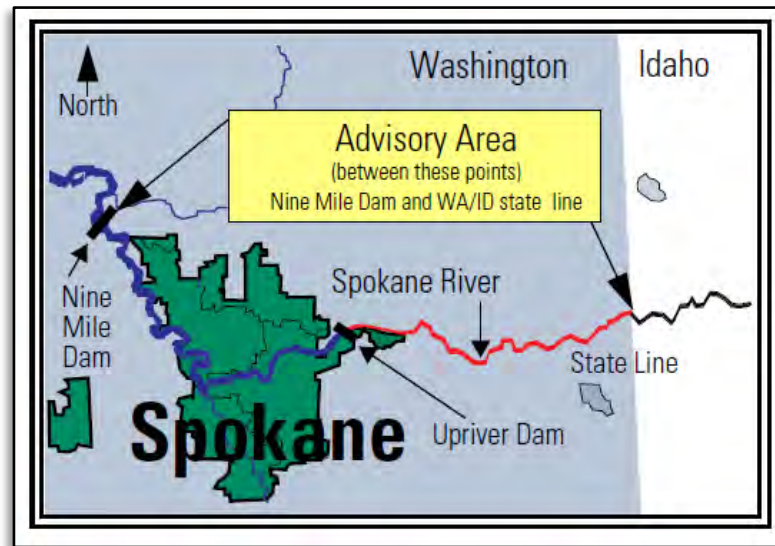
6.1. 2001: Health Advisory for Spokane River Fish Consumption

The first Spokane River warning about eating PCB-contaminated fish was issued in March 2001 (USGS 2001) as a health advisory by WDOH/Spokane Regional Health District (SRHD). This advisory was well-supported by numerous sampling and analysis studies conducted and published in the 1990s by the U.S. Geological Survey (USGS) (Smith et al. 1988, Maret and Skinner 2000, Maret and Dutton 1999)^{2,12,13} and WDOE (Golding 1996, Johnson 1999, Kadlec 2000, and Serdar 1999).¹⁴⁻¹⁷ These studies consistently showed fish had bioaccumulated very high concentrations of PCBs and, to a lesser extent, heavy metals. Contaminants were analyzed in fish tissue for three fish species caught in two parts of the upper Spokane River.

USGS summarized the data in a short 2001 report: *PCBs in Tissue of Fish from the Spokane River, Washington*, to which the 2001 WDOH advisory *Health Advisory for Spokane River Fish Consumption* was attached.¹⁸

This first WDOH/WSRHD Health Advisory was developed to instruct residents who fished in the two impacted river sections as shown in 0 to limit their consumption of fish.

Exhibit 5. Health Advisory: Map Showing Impacted Spokane River Sections



Source: Health Advisory for Spokane River Fish Consumption. Update, March Update 2001, WDOH/WSRHD.¹⁸

The Health Advisory specifically recommended limiting the frequency of meals for rainbow trout, mountain whitefish, and largescale suckers based on a typical 8-ounce (28 g) fish meal. (See 0.). A complete updated list of fish advisories can be found on WDOH's website.

Exhibit 6. Health Advisory: Suggested Fillet Meal Limits

Fish Species	Recommendation
Above Upriver Dam to WA / ID state line	
Rainbow trout	None
Mountain whitefish	None
Largescale suckers	One meal per month
Below Upriver Dam to Nine Mile Dam	
Rainbow trout	One meal per month
Mountain whitefish	One meal every other month
Largescale suckers	One meal per month
Note: One meal equals 8 ounces of fish for the average adult. Meal sizes are assumed to be less for children.	

Source: Health Advisory for Spokane River Fish Consumption. Update, March Update 2001, WDOH/WSRHD.¹⁸

6.2. Fish Consumption Advisories

As shown in 0, the PCB fish tissue concentration was so high that WDOH/SRHD advised a total ban on consumption of Rainbow Trout and Mountain Whitefish and limited consumption of largescale suckers to one meal per month for areas of the river stretching from the Idaho border to the Upriver Dam.

ATSDR/WDOH has placed an even tighter restriction on current fishing, with a catch-and-release order imposed on all fishing in this river stretch, with a total consumption ban now in place for all fish species.

The recommended fish consumption from the Upriver Dam to the Nine Mile Dam was also strictly limited to just one fish meal per month or every other month for each of the species. The current ATSDR/WDOH fish advisory has modified the 2001 consumption advisory to about one more fish meal a month or every other month for each species, with another group of contaminants—polybrominated diethyl ethers—added to the list of compounds of concern.

The above 2001 fish consumption advisory indicates that, while the Spokane River section located near the city of Spokane has seen a slight improvement over the last 20 years or so, the fish tissue concentrations of PCBs and lead (Pb) remain a threat to human health.

It should be noted that this first consumption advisory was intended to warn the public about the number of meals that were safe for both PCBs and Pb, and it focused on the same fish species that were sampled in the 1999 USGS/WDOH report—namely, rainbow trout, mountain whitefish, and largescale suckers. My review of the supporting fish tissue data support a fishing advisory for PCBs with regard to eating fillets. The warning for Pb exposures only seems to have been applied as a precaution for consuming the nonedible parts of the fish and was thus issued for eating the whole fish.

While the fish advisory applied to both whole fish and fillets for PCB contamination, the health advisory also noted that there was a potential health threat from Pb-contaminated fish, but that only applied to consuming whole fish. It did not apply to fish fillets, as stated in the following section of the Health Advisory:

What are the harmful effects of PCBs and lead? Who should be concerned? Pregnant women and women considering pregnancy should carefully follow the meal limits given in table 1.

*The fetus is particularly susceptible to the harmful effects of lead and PCBs when the mother eats contaminated fish. Such effects can include learning problems that appear during childhood years. Negative effects on a child's behavior and ability to learn can also occur in children exposed to lead from birth through six years of age. **Because lead was found at higher levels in whole fish samples, it is especially important for children under age six to eat only fillets according to the meal limits in table 1.** [original emphasis]*

As the Health Advisory emphasis indicates, Pb was only a concern when consuming whole fish. The reason for this distinction is that, unlike PCBs, which are bioaccumulated in all fat-containing tissues and organs in fish, Pb is not. After Pb is absorbed by fish, it is sequestered and stored in nonedible fish parts such as the gills, bone, kidney, spleen, and intestines. It is largely sequestered into bone, where it substitutes for calcium. This type of absorption and sequestration into bone is similar to how the human body stores Pb. Consequently, and most importantly, Pb does not bioaccumulate in fish muscle tissue, so the only concern with Pb in typical fish advisories pertains to eating the whole fish—including bone and gills. This opinion is supported by the detailed analysis later addressed and carefully analyzed in the 2007

ATSDR/WDOH Health Consultation (ATSDR 2007) for Spokane River fish in which a determination was made to eliminate Pb as a chemical of concern, and it was shown that consuming fish fillets would not pose a health threat (i.e., muscle tissue fillets contain 10 times less Pb than the nonedible whole fish body parts).

USGS studies demonstrate that Pb does not bioaccumulate in fish fillets from the Spokane River. The 1989 USGS study,¹³ published 2-years before the 2001 Health Advisory,¹⁸ showed fish analyzed from Spokane River sections known to be downstream of mining production sites had insignificant bioaccumulation of any heavy metal, including Pb in fillet muscle tissue. In fact, the USGS showed there was a “poor correlation” between the paired highly contaminated heavy metal sediments in mining areas (save for Cd) and the corresponding fish tissue levels in those areas. The study stated:

Correlations between most trace-element concentrations in bed sediment and tissue (livers and fillets) were poor; however, there was a significant correlation between Cd in bed sediment and liver tissue. Trace-element concentrations in bed sediment did not appear to be good predictors of concentrations in tissue...

In addition to discussing the very important concept that heavy metals did not bioaccumulate in fish, USGS (1989) showed that the fish tissue levels—even in highly enriched sediments—were below the U.S. EPA sediment screening values (SV) that were developed for bed sediments and edible fish tissue. (SVs were defined as “associated adverse effects to aquatic life or human health are possible, but expected infrequently”; U.S. EPA tissue SVs were protective of human health at a “1 X 10⁻⁵ risk factor” based on an average-sized adult [70 kilograms] and a consumption rate of 6.5 grams of fish per day [or approximately 45 grams of fish per week]). The researchers stated:

Even though many of the sites exhibited trace-element enrichment, no trace-element concentrations in sportfish fillets exceeded U.S. EPA SVs. This is noteworthy, because Pb and Hg can bioaccumulate in aquatic biota and are pollutants of concern around mining sites in the study area. It is apparent from this study that trace elements in bed sediment are not readily bioavailable for uptake by fish, especially the trace elements As, Cd, Pb, Hg, and Se, which are known to bioaccumulate in aquatic food chains.

Finally, even in areas in which the riverbed Pb sediments were greatly enriched to levels higher than 100 ppm, no Pb bioaccumulation was seen in fish livers or fillets:

Although concentrations of Pb were high (>100 µg/g) in bed sediment at some NROK [Northern Rockies Intermontane Basins] sites, Pb did not tend to accumulate in fish

livers or fillets. This finding is particularly important because Pb has been identified as a pollutant of concern to humans and wildlife as a result of mining activities in this study area.

The WDOH/SRDH warning not to eat whole fish because of Pb does not apply to PCB-contaminated fish. This is because PCBs are sequestered into all tissues and organs that contain fat (or adipose). When PCB are ingested by fish, they bioaccumulate in all fat-containing tissue, which include the edible parts of fish—namely, the fish fillets (muscle). Although fish is often served with skin attached (minus the scales), WDOH recommends removing the skin and the attached adipose tissue to *reduce* PCB exposures.

Because PCBs bioaccumulate in all fat-containing tissues and organs, fish fillets can still contain high levels of PCBs even after the skin and adipose tissues are removed during meal preparation to reduce PCB exposure. This is because muscle contains both *intermuscular* and *intramuscular* fat. Intermuscular fat is defined as any fat (including the fat between muscle groups and within a muscle) found beneath the muscle fascia (which attaches, stabilizes, encloses, and separates individual muscles from one another and also from other internal organs). Intramuscular fat is the visible fat found within an individual muscle.

In its 1999 study, USGS (Maret and Dutton 1999) confirmed that not only were the PCB levels in Spokane River fish tissue fillets significantly elevated but that they were the highest recorded in the Northern Rockies Intermontane Basins (NROK) study area (defined as a 31,500-square-mile area in western Montana, northern Idaho, and northeastern Washington), stating:²

Concentrations in most fillet samples of sportfish collected at Spokane River sites during 1993–96 also exceeded the U.S. EPA screening value for the protection of human health. Samples from this area contained the highest PCB concentrations in the NROK study area. One whole-fish composite (largescale sucker) collected in 1993 from the Spokane River above Upriver Dam (table 3; site 25) contained a total PCB concentration of 2.78 µg/g. In comparison, the 85th percentile for total PCBs in whole fish analyzed for the NAWQA Program during 1992–94 was 0.356 mg/g (table 7). [Maret and Dutton 1999]

USGS also concluded that the total PCB levels determined in the previous 1993 WDOE study (published in 1994)¹⁹ were likely underestimated because the analysis did not include all Aroclors:²

In addition, because the WDOE study included the tissue analyses of only three arochlors [sic] (PCB 1248, 1254, and 1260), an analysis of total PCBs similar to that used in the NAWQA Program would have resulted in higher reported concentrations.

This initial WDOE study pointed to specific river locations as potential PCBs release sites:²

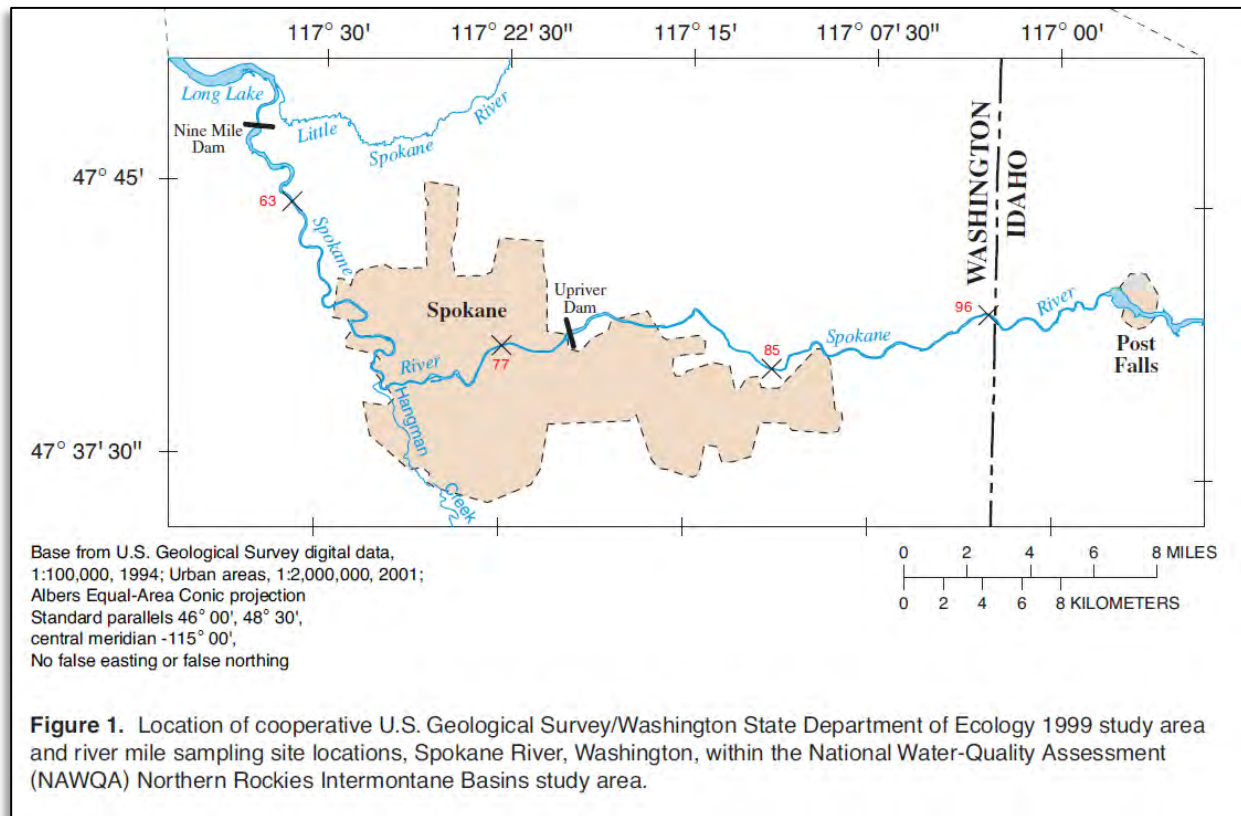
On the basis of concentrations of these three arochlors[sic] in tissue, the WDOE (1995) identified the PCB sources as primarily industrial and wastewater treatment facilities (fig. 4 and table 2) in and around the city of Spokane, and the Kaiser Aluminum and Old Inland Pit Superfund sites (fig. 3; sites 9 and 14). In addition, the WDOE (1996) identified PCBs as one of the contaminants responsible for impaired uses on the Spokane River in their 305(b) water-quality status report. However, there is currently no State fish consumption advisory for the Spokane River.

The USGS/WDOE 1999 study revealed that the PCB concentrations in sportfish were between 13 and more than 300 times the safe level for edible fish tissue for human consumption (the levels were also in excess of safe fish tissue concentration for fish-eating wildlife). The USGS/WDOE report summarized this as follows:²

A cooperative study between the U.S. Geological Survey (USGS) and the Washington State Department of Ecology (WDOE), completed in July 1999, documented elevated concentrations of polychlorinated biphenyls (PCBs) in sportfish (rainbow trout and whitefish) and large-scale suckers in the Spokane River, northeastern Washington. Concentrations of PCBs in fillets of sportfish collected from four sites on the Spokane River ranged from 0.07 to 1.61 parts per million (ppm)—1 part PCB to 1 million parts of tissue). These concentrations exceed the human consumption criterion of 0.0053 ppm for edible fish tissue. Concentrations of total PCBs in most of the rainbow trout (whole body and fillets) and largescale sucker (whole body) samples exceed the criterion of 0.11 ppm for fish-eating wildlife. When these data are added to data from previous studies during 1993–94 and 1998–99, it is evident that concentrations of PCBs in fish have remained 10 times higher than the criteria for more than 6 years.

0 presents the sampling locations for the Spokane River fish (USGS 1999):²

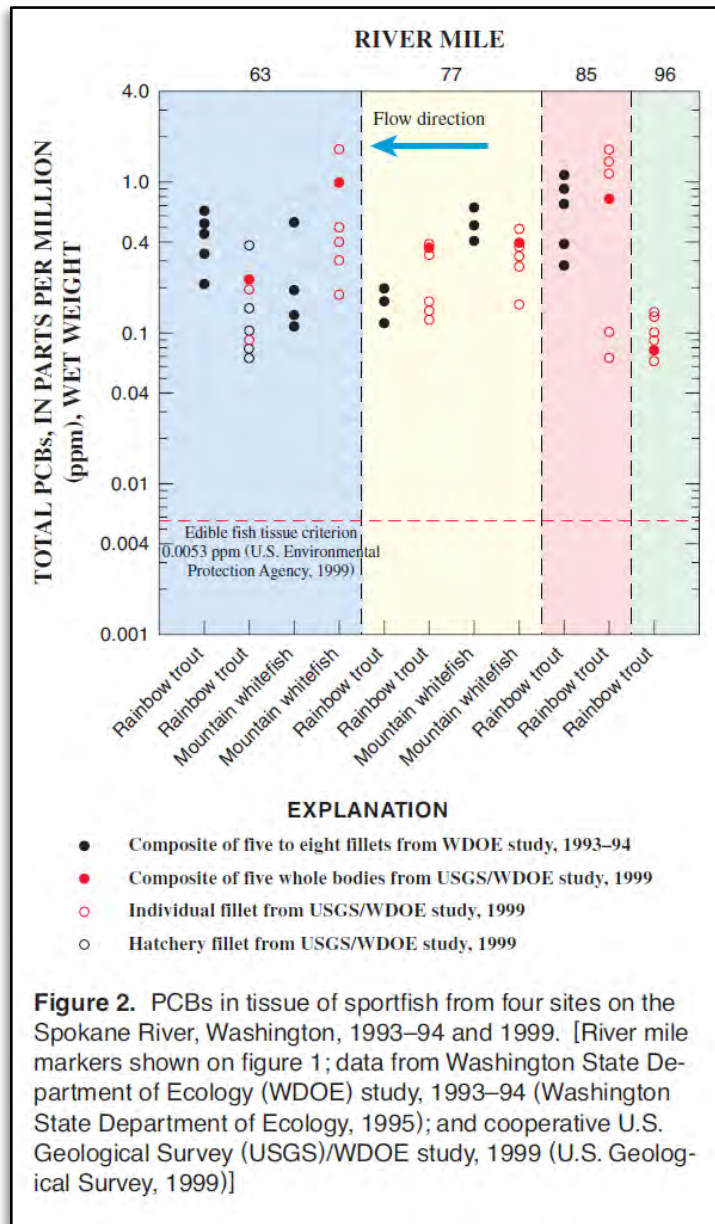
Exhibit 7. 1999 USGS Sampling locations for Spokane River Fish



Source: Maret R and Dutton D. *Summary of Information on Synthetic Organic Compounds and Trace Elements in Tissue of Aquatic Biota, Clark Fork-Pend Oreille and Spokane River Basins, Montana, Idaho, and Washington, 1974–96, 1999.* Water-Resources Investigations Report 98–4254. National Water-Quality Assessment Program.²

As shown in 0, all fish tissue samples that had been analyzed for total PCBs as of 1999 had levels that far exceeded U.S. EPA's safe "edible fish tissue criterion" for human consumption of 0.0053 ppm:

Exhibit 8. PCB Concentrations in Sportfish



Source: Maret R and Dutton D. *Summary of Information on Synthetic Organic Compounds and Trace Elements in Tissue of Aquatic Biota, Clark Fork-Pend Oreille and Spokane River Basins, Montana, Idaho, and Washington, 1974–96, 1999.* Water-Resources Investigations Report 98–4254. National Water-Quality Assessment Program.²

The study also specifically noted that the Spokane River was contaminated “about 100 times greater than more pristine streams in Washington:”

Summary of Findings

Total PCB concentrations in tissue samples of sport-fish collected from four sites on the Spokane River during the 1993–94 and 1999 studies are summarized in figure 2.

Concentrations in all fish fillets and whole-body sportfish exceeded the edible fish tissue criterion of 0.0053 ppm. In fact, the concentrations of PCBs in fish tissue were 10 times higher than the criterion and have been at this level for the past 6 years. Concentrations were highest in rainbow trout fillets collected in 1999 behind Upriver Dam at river mile 85. The PCB concentrations in Spokane River fish were about 100 times higher than those in more pristine streams in Washington (Serdar, 1999).

All subsequent studies have confirmed that PCB levels in edible fish tissues have remained high since the first WDOH/SRDH fish advisory was issued and have consistently reaffirmed the public must be warned that the PCB fish tissue levels continue to pose a high risk level of illness and disease requiring that fishing advisories be issued to warn the public of the dangers of eating Spokane River fish—even today. This is because PCBs are extremely persistent and recalcitrant to degradation in the environment.

6.3. ATSDR/WDOH Health Advisories for the Spokane River

The goal of this section is to provide supporting evidence for my opinion that the Washington State Department of Health has taken prudent and well-founded action by issuing (in collaboration with SRHD and ATSDR) its fish consumption advisories to protect public health. The warnings it has issued to residents (if followed) should result in the safe consumption of PCB-contaminated fish. The following summarize my opinions based on the information I present in this section:

1. The ATSDR/WDOH fish advisories are based on generally accepted toxicological/risk assessment methods and protocols for determining the safe consumption rates of PCB-contaminated fish.
2. The ATSDR/WDOH fish advisories throughout the years have been consistent and scientifically tenable, relying on the best available measurements of fish tissue PCB data, as well as toxicological and exposure information available at the time.

3. The ATSDR/WDOH fish advisories provide simple and vital health information that is easily understood by the general public and answers the most important question regarding eating PCB-contaminated fish: How much fish can I and my family safely eat?
4. The WDOH is the *state* agency that is responsible for protecting the health of Washington state residents, and ATSDR is the lead *U.S. governmental* agency responsible for protecting public health; together they are most qualified to determine the acceptable risk level and fish consumption rates of PCB-contaminated fish.
5. If Washington residents follow the fish consumption recommendations issued by ATSDR/WDOH, eating PCB-contaminated fish will pose *de minimis* risks (which are negligible), and no PCB-related illness or disease (including cancer) should develop in the exposed population.

6.4. Summary of ATSDR/WDOH Health Consultations for PCB-Contaminated Spokane River Fish

There have been three ATSDR/WDOH Health Consultations to evaluate the health risks posed by consuming PCB-contaminated fish caught at different times and locations along the Spokane River. However, the WDOH/SRDH 2001 State fish advisory only applied to a very limited part of the river (from the Idaho/Washington border to the 9 Mile Dam). Fish samples continued to be analyzed for PCBs in the following years, and health concerns were raised regarding eating fish caught in other parts of the river as PCB-contaminated sediments were transported and recreational fishing increased. Due to the concern that fish tissue levels of PCBs downriver from the 9 Mile Dam downstream could also pose a health threat, WDOE requested that ATSDR and WDOH conduct a more thorough investigation in which the historical fish tissue data was reviewed which was augmented with and additional samples.

6.5. 2005 ATSDR/WDOH Health Consultation

The first ATSDR/WDOH Health Consultation for the Spokane River,⁴ was completed in 2005 in response to a WDOE request and an earlier recommendation in the 2001 WDOH/SRHD fish advisory. The purpose was to review and evaluate “possible health risks from exposure to PCBs through consumption of Long Lake fish.” This was deemed important because the SRHD’s fish consumption survey of Spokane-area residents that showed “Long Lake to be the primary recreational fishing area for anglers in the greater

Spokane area.” In addition, the Agencies noted that the previous WDOH/SRDH 2001 fish advisory that was discussed was amended, but only for PCBs:

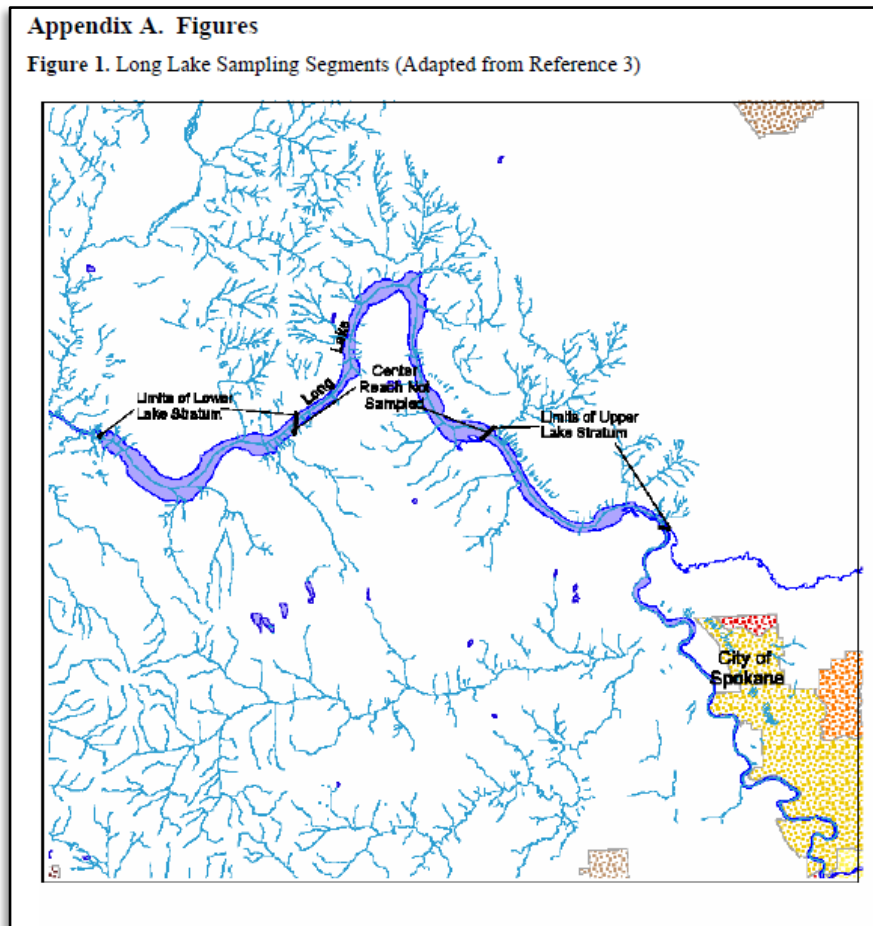
In conjunction with this evaluation, the existing fish consumption advisory released in March 2001 for upstream portions of the river has been revised. The revisions segment the river into three portions, including Long Lake. For upstream reaches of the Spokane River, DOH recommends no consumption of fish caught between the Idaho border and Upriver Dam, and advises a limit of one meal per month for fish caught between Upriver Dam and Nine Mile Dam. As noted below in the Recommendations section of this document, the Long Lake segment does not require meal limits, but anglers are advised to prepare and cook fish caught in Long Lake in a manner that will reduce PCB levels.

One of the goals of the study was to determine if there was a spatial pattern of PCB-contaminated fish in Long Lake. It was assumed that, because historical PCB fish tissue samples were highly contaminated with PCBs in the upper part of Spokane River (above the Upriver Dam which prompted the 2001 WDOH/SRDH fish advisory), there could likewise be a decreasing gradient of PCB contamination traveling downstream for Long Lake (starting at the Little Spokane River confluence) as PCB-contaminated sediments are transported farther downriver. To test this hypothesis, fish tissue samples were analyzed in the upper and lower sections of Long Lake:⁴

The most recent sampling of Long Lake took place in June 2001 when Ecology, in coordination with the Washington Department of Fish and Wildlife, collected samples from an upper and lower region of the lake. Three composite samples for each of five species were gathered from the upper region that covers a 5.7-mile stretch downstream of the Little Spokane River confluence. Three composites of the same species were taken from the lower region of the lake that spanned 6.2 miles upstream from Long Lake Dam.

The upper and lower sampling areas are presented in Exhibit 9.

Exhibit 9. Upper and Lower Sampling Areas



Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

A comparison of the compiled fish data indicates that a spatial pattern did not exist. As shown in Exhibit 10, the PCB concentrations (based on Aroclor analysis) from the two discretely sampled upper and lower segments (which were widely separated) were not significantly different. That is, the fish tissue PCB levels did not appreciably decrease downstream in Long Lake.

Exhibit 10. PCB Concentrations in Fish Sampled in 2001

Table 1. Total Polychlorinated Biphenyl (PCB) Concentrations In Fish Sampled In 2001 From Long Lake, Spokane County, Washington.

Location	Species	Tissue	Samples	# per composite	Total PCBs (ug/kg)		
					Mean	Min	Maximum
Upper Long Lake	Largemouth bass	Fillet	3	10	50	39	72
	Largescale sucker	Fillet	3	10	110	86	132
		Whole ^a	3	NA	265	164	336
	Mountain whitefish	Fillet	3	6	73	60	89
	Smallmouth bass	Fillet	3	5	42	32	54
	Yellow perch ^b	Fillet	3	10	<11	NA	<11
Lower Long Lake ^c	Largemouth bass	Fillet	3	4	56	47	64
	Largescale sucker	Fillet	3	9	92	63	112
		Whole ^a	2	NA	357	321	393
	Smallmouth bass	Fillet	3	5	31	17	39
	Yellow perch ^b	Fillet	3	11	<11	NA	<11

Note: PCB totals are calculated as the sum of Aroclors 1248, 1254, 1260 from composite samples.
a = Whole samples were analyzed from individual fish.
b = All Aroclors were below detection in yellow perch. Detection limits reported in yellow perch for each Aroclor were either 10 or 11 ug/kg.
c = Mountain whitefish are not found in the lower region of the lake.
ug/kg = micrograms per kilogram also known as parts per billion (ppb).

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

While the PCB data shown in Exhibit 10 are based on total PCBs using Aroclor analysis (summed Aroclors: 1248, 1254, and 1260), samples were also analyzed for 12 specific PCB congeners. These 12 PCB congeners are called the World Health Organization (WHO) dioxin-like congeners. In 1998, WHO identified 12 specific congeners that produced dioxin-like toxicity. Toxic equivalency factors (TEFs) were adopted for each of the 12 PCB congeners by a consensus of WHO scientific experts. The TEF is a cancer potency value assigned to each of the WHO congeners and represents the relative toxicity of the

PCB congener compared to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) which is the most toxic/carcinogenic dioxin-like compound in the group of dioxin-like compounds and is also the most carcinogenic compound U.S. EPA has ever studied. The Agency has derived cancer potency values for approximately 230 carcinogenic compounds; as shown in Exhibit 11, TCDD is the most carcinogenic compound. The *second* and *fourth* most potent carcinogenic compounds (of the 230 carcinogens) are PCBs 126 and 169. In fact, the four most carcinogenic compounds are dioxin-like compounds, and PCB 126 is about 24-times more carcinogenic than nearest compound that is not one of the dioxin-like congeners (1,2-dimethylhydrazine).

**Exhibit 11. Ranking Carcinogenic Potency:
U.S. EPA's Approximately 230 Carcinogenic Compounds**

Cancer Slope Factor (Potency)	Compound Name
130000.00	TCDD
13000.00	PCB 126 (Pentachlorobiphenyl, 3,3',4,4',5)
6200.00	Hexachlorodibenzo-p-dioxin, Mixture
3900.00	PCB 169 (Hexachlorobiphenyl)
550.00	1,2-Dimethylhydrazine

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

Due the extreme carcinogenic potency of the dioxin-like PCB congeners, it was prudent for ATSDR/WDOH to calculate the dioxin-like concentration in fish tissue. This concentration is calculated by multiplying the PCB congener specific TEF (which represents the carcinogenic potency of each of the 12 WHO congeners relative to TCDD) by the concentration detected in fish tissue. The calculated products for each of the 12 PCB congeners are summed to calculate the total dioxin-like equivalent (PCB-TEQ) concentration for the fish sample. The PCB-TEQ concentrations for each fish species in upper and

lower Long Lake sections are presented in Exhibit 12. The PCB-TEQ concentrations, like the total PCB Aroclor concentrations did not differ significantly between the two different parts of Long Lake.

Exhibit 12. PCB Toxic Equivalent Concentrations in Fish

Table 2. Polychlorinated Biphenyl (PCB) Toxic Equivalents (PCB-TEQ) Concentrations in fish Sampled In June 2001 From Long Lake, Spokane County, Washington.

Location	Species	Tissue	Samples	# per composite	Result (ng/kg)		
					Mean	Min	Maximum
Upper Long Lake	Largemouth bass	Fillet	3	10	1.7	1.2	2.4
	Largescale sucker	Fillet	3	10	3.1	2.8	3.5
	Mountain whitefish	Fillet	3	6	2.0	1.6	2.2
Lower Long Lake	Largemouth bass	Fillet	3	4	2.1	1.6	2.7
	Largescale sucker	Fillet	3	9	2.2	1.2	2.7

Note: PCB-TEQs are calculated using the toxic equivalency factors adopted by the World Health Organization in 1998. For all samples, congeners 105,114,118,126, and 156 made up 97 - 98% of the total PCB-TEQ.
ng/kg = nanograms per kilogram, also known as parts per trillion (ppt).

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

6.6. Health Risk Assessment

Based on the contaminant data detected in edible fish tissue, ATSDR/WDOH conducted a health risk assessment to determine if those levels posed a noncancer health hazard or carcinogenic risk based on average and high-end consumption rates. To provide consistency with early studies, the Agencies stated that it “follows the same methodology used to establish the current fish consumption advisory for the Spokane River.”

6.7. PCBs

For noncancer health hazards, fish contaminated with PCBs posed a hazard risk only for those who ate many meals—except for largescale sucker species, for which the safe level was more than eight times the health protective level (even at an average consumption rate of 42 g/day). For high-end consumption rates (90 g/day; those eating the most fish) the health hazard was much higher. with consumption of largescale suckers exceeding a safe level by 25-fold. ATSDR stated (2005):⁴

While the doses estimated for the average consumer exceed the MRL for most fish species, they are not very much above the MRL. Hazard quotients calculated for exposure to PCBs in Long Lake fish ranged from 0.5 for average consumers of yellow perch to 8.5 for high-end consumers of largescale sucker fillets. High-end consumption of whole largescale sucker at the maximum detected level results in a hazard quotient of 25.3 (Appendix D, Table D2).

In contrast to noncancer health hazards, in which the threat, for the most part, was limited to eating largescale suckers, the cancer risk associated with consumption of PCB-contaminated fish exceeded the *de minimis* cancer risk for both average and high consumers for all fish species. Furthermore, the *de minimis risk* cancer risk levels were exceeded in both upper and lower sections of Long Lake. The summary hazard quotients and cancer risk for fish are shown in 0. The highest cancer risk was for those high-end consumers of PCB-contaminated largescale suckers, which posed a cancer risk more than 100 times the *de minimis* risk level.

Exhibit 13. Health Risk Calculations from Exposure to Total PCBs in Fish

Table D2. Health Risk Calculations from Exposure to Total Polychlorinated Biphenyls in Fish Sampled in 2001 from Long Lake, Spokane County, Washington

Location	Species	Tissue	# of Samples	Hazard Quotient		Cancer Risk	
				Average	High-end	Average	High-end
Upper Long Lake	Largemouth bass	Fillet	3	1.5	4.6	3E-05	8E-05
	Largescale sucker	Fillet	3	3.3	8.5	6E-05	1E-04
		Whole ^a	3	7.9	21.6	1E-04	2E-04
	Mountain whitefish	Fillet	3	2.2	5.7	4E-05	1E-04
	Smallmouth bass	Fillet	3	1.3	3.5	2E-05	6E-05
	Yellow perch	Fillet	3	0.5	1.1	8E-06	2E-05
Lower Long Lake	Largemouth bass	Fillet	3	1.7	4.1	3E-05	7E-05
	Largescale sucker	Fillet	3	2.8	7.2	5E-05	1E-04
		Whole ^a	2	10.7	25.3	2E-04	4E-04
	Smallmouth bass	Fillet	3	0.9	2.5	2E-05	4E-05
	Yellow perch	Fillet	3	0.5	1.1	8E-06	2E-05
Lower and Upper Long Lake	Largemouth bass	Fillet	6	1.6	4.6	3E-05	8E-05
	Largescale sucker	Fillet	6	3.0	8.5	5E-05	1E-04
		Whole	5	9.0	25.3	2E-04	4E-04
	Smallmouth bass	Fillet	6	1.1	3.5	2E-05	6E-05
	Yellow perch	Fillet	6	0.5	1.1	8E-06	2E-05

Numbers in **bold** are those that do not exceed a hazard quotient of 1.

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

Similarly, the cancer risks for the 12 WHO dioxin-like PCB congeners exceeded the *de minimis* risk level for all fish and consumption rates for both upper and lower Long Lake, as shown in Exhibit 14.

Exhibit 14. Health Risk Calculations from Exposure to PCB-TEQs in Fish

Table D4. Health Risk Calculations from Exposure to Polychlorinated Biphenyl Dioxin Toxic Equivalents (PCB-TEQs) in Fish Sampled in 2001 from Long Lake, Spokane County, Washington

Location	Species	Tissue	# of Samples	Hazard Quotient		Cancer Risk	
				Average	High-end	Average	High-end
Upper Long Lake	Largemouth bass	Fillet	3	1.0	3.1	7E-05	2E-04
	Largescale sucker	Fillet	3	1.8	4.4	1E-04	3E-04
	Mountain whitefish	Fillet	3	1.1	2.9	7E-05	1E-04
Lower Long Lake	Largemouth bass	Fillet	3	1.2	3.5	8E-05	2E-04
	Largescale sucker	Fillet	3	1.3	3.5	8E-05	2E-04
Lower and Upper Long Lake	Largemouth bass	Fillet	6	1.1	3.5	7E-05	2E-04
	Largescale sucker	Fillet	6	1.5	4.4	1E-04	3E-04

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

6.8. Heavy Metals

In addition to PCBs, a limited number of fish were analyzed for heavy metal contamination. These analytes were included in the USGS study conducted in 1999 (discussed previously) for fish caught upriver from the Nine Mile Dam to the Idaho border. The four heavy metals of concern were zinc, cadmium, lead, and mercury. USGS found that lead and cadmium were not detected, and zinc was dismissed as an essential human element. Regarding human health concerns, USGS stated:

A more limited analysis for metals, including zinc, cadmium, lead, and mercury, was also performed on the June 2001 Long Lake fish samples. Lead and cadmium were not detected in any sample with a detection limit of 100 parts per billion (ppb) (i.e., lead and cadmium were not detected above 100 ppb). While detections of zinc are relevant for ecological assessment, they are not a concern for human health and will not be discussed or evaluated in this health consultation.

The only toxic heavy metal of concern was mercury (Hg) but, even with high consumption rates, the hazard only slightly (i.e., 0.7) higher than 1.0, which is the *de minimis* noncancer health hazard, and this was for exposure to a fetus *in utero*. USGS summarized its findings as follows:

Estimated doses of mercury for the average consumer of largemouth bass from Long Lake are below the EPA RfD, with hazard quotients of 0.7 for the upper lake and 0.6 for the lower lake. High-end exposure estimates give doses only slightly higher than the RfD, with hazard quotients of 1.6 and 1.7 for the upper and lower lake, respectively. This comparison indicates that exposure to mercury in largemouth bass from Long Lake is not a health concern for the average consumer and only of minimal concern for high-end consumers. It is important to note that the dose comparisons given here for mercury relate to in utero exposure and are not relevant to the general population but pertain to women of child-bearing age and children under 6 years of age. Other endpoints of mercury toxicity are not of concern at these levels of exposure.

6.9. Fish Consumption Advisory

To develop the fish consumption advisory, ATSDR/WDOH evaluated the *combined* toxicity of PCBs and mercury, which focused on the only two chemicals of concern—PCBs and Hg—that exceeded health thresholds in their risk assessment. It should be noted that even though PCBs posed very high cancer risks, the agencies based their fish consumption advisory on noncancer health hazards. Although the Agencies did not present separate tables for fish consumption rates for PCBs apart from Hg, it is apparent that the fish advisories listed for small mouth bass, Largemouth Sucker, Mountain Whitefish, and Yellow Perch are all based on PCB-contaminated fish. This is because ATSDR/WDOH only analyzed Hg in Largemouth Bass. The recommended fish meal consumption rates are presented in 0.

Exhibit 15. Meal Limits Based on PCBs and Mercury**Table 7.** Meal Limits Based on PCBs, Mercury, Long Lake Fish, Washington.^a

Fish Species	Recommended 8-ounce meals per month	
	Developmental ^b	Immune ^c
Large Mouth Bass	3	3.2
Small Mouth Bass	6.5	5.1
Largescale Sucker	2.4	1.8
Mountain Whitefish	3.3	2.6
Yellow Perch	Unlimited	Unlimited

a= Large mouth bass were the only species sampled for mercury

b = Based on developmental endpoint of PCBs and mercury assuming a female body weight of 60 kg

c = Based on the Immune endpoint of PCBs, assuming an adult body weight of 70 kg

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Evaluation. Evaluation of Polychlorinated Biphenyls (PCBs) in Fish from Long Lake (also known as Lake Spokane) Spokane County, Washington. April 25, 2005.⁴

It should be noted that the ATSDR/WDOH fish advisory does not account for the noncancer health hazards from dioxin-like PCBs. This is not because they do not produce noncancer toxicity, but rather because no health agency (including ATSDR, WDOH, or U.S. EPA) has yet derived a toxicity value that can be used to calculate noncancer health hazards or fish consumption advisories. This is because exposure to background levels of dioxin-like compounds is *already* so high that even background concentrations pose a health hazard (USEPA 2003). Obviously, any additional exposure to dioxin-like compounds, which would include the dioxin-like PCB congeners measured in the Spokane fish, would pose health hazards far exceeding even the hazardous background levels. ATSDR/WDOH highlighted these issues:

EPA is not proposing an RfD for dioxins and dioxin-like compounds. The agency states in its draft reassessment that “any RfD that the Agency would recommend under the traditional approach for setting an RfD is likely to be 2–3 orders of magnitude (100 to 1,000 times) below current background intakes and body burdens.” Comparison with

background is, therefore, an essential step in evaluating site-specific exposures to dioxins, including dioxin-like PCBs.

It should be stressed that because the fish advisory is based solely on *noncancer* health hazards, Washington residents can safely eat the number of fish meals recommended in Exhibit 15. However, if ATSDR/WDOH based their recommendations on *de minimis cancer* risks from PCBs (as Hg is not a carcinogen), a total ban on eating any fish could be warranted to protect Washington residents from developing cancers.

Finally, ATSDR/WDOH issued its overall conclusions:

Conclusions

- 1. Average consumers of sport fish from Long Lake are not expected to experience adverse health effects from exposure to contaminants in those fish. No apparent public health hazard exists for average consumers of Long Lake sport fish.*
- 2. High-end consumers of sport fish from Long Lake might be exposed at doses only slightly above health comparison values.*
- 3. Although these doses are not expected to cause adverse health effects, prudent public health measures such as cooking and cleaning fish to reduce exposure to PCBs through fish consumption can lower potential risk associated with PCBs in fish.*

6.10. 2007 ATSDR/WDOH Health Consultation

In 2007, at the request of the WDOE and the SRHD, ATSDR conducted a Health Consultation for several contaminants to determine if they posed a health threat from eating Spokane River fish. Results were published in *Evaluation of PCBs, PBDEs and Selected Metals in the Spokane River, Including Long Lake Spokane*, August 28, 2007.⁵ ATSDR and WDOH noted that, while fish tissue concentrations of contaminant were lower in 2005, it was not likely due to natural attenuation but to action taken to remove contaminated river sediments in upriver sections of the Spokane River. ATSDR/WDOH suggested that further monitoring of fish tissue levels would be necessary to ultimately confirm that remedial actions were effective in lowering fish tissue levels, which would then allow residents to eat more fish:

Ecology suggests that lower levels of PCBs in fish from Upriver Dam to the Idaho border correlate with cleanup actions in the Spokane River. To verify this observation, Ecology

and DOH concur that further monitoring of the Spokane River is appropriate to confirm this apparent trend and before changing the original fish advisory.

6.11. Summary Conclusions: PCBs Pose a Public Health Hazard

After careful analysis of the fish tissue data for the three contaminants of concern—namely, PCBs, PBDE, and Pb—only PCBs posed a public health hazard:⁵

Conclusions

Exposure to PCBs through ingestion of Spokane River fish caught in the Spokane River represents a public health hazard. The potential for adverse health effects to result from eating Spokane River fish depends on several factors such as amount of fish consumed and fishing location.

- *Consumption of rainbow trout and mountain white fish in Ninemile Dam to Upriver Dam is a public health hazard.*
- *Recent samples of resident fish in the Spokane River showed levels of PCBs that are lower than previous samples except for mountain whitefish and rainbow trout fillets and largescale suckers in whole body samples at Mission Park.*
- *Eating frequent meals of trout and mountain whitefish that live in the Spokane River may cause health problems, particularly to children, infants and pregnant women. PCBs in these fish may affect the immune system and cause learning problems in children exposed in the womb.*

Extremely high levels of PBDEs were observed in mountain whitefish and rainbow trout (whole) between Ninemile Dam to Upriver Dam. Due to limited research on the possible consumer health risk from PBDEs, DOH concludes a no apparent public health hazard exists. However, concern remains about the effects of these compounds on humans and biota.

- *It is important to consider PBDEs for future health advisories since there may be potential health risks associated with fish consumption.*

A public health hazard exists for pregnant women and children who consume whole fish contaminated with lead from the Spokane River between the Upper Long Lake and the Idaho Border (Stateline). No public health hazard exists for adults exposed to lead who consume fillets from the Spokane River. [emphasis added]

While the previous ATSDR/WDOH (ATSDR 2001, 2005) fish consumption advisories identified Pb as a compound of concern this more recent analysis included it but did not find it rose to a health hazard.^{4,18} For Pb, ATSDR/WDOH essentially reiterated the opinion I stated previously regarding the Pb health assessment in the ATSDR 2001 Health Consultation: fish Pb tissue levels only pose a health hazard when

the whole fish (including the typically nonedible fish bones, gills, liver, etc.) is eaten. In addition, the hazard only applies to pregnant women and young children (less than approximately 6 years of age). It does not apply to those eating fish fillets. Furthermore, as was stated earlier, it only applies to the stretch of the Spokane River from upper Long Lake to the Idaho border:

A public health hazard exists for pregnant women and children who consume whole fish contaminated with lead from the Spokane River between the Upper Long Lake and the Idaho Border (Stateline). No public health hazard exists for adults exposed to lead who consume fillets from the Spokane River. Women who are pregnant or planning a pregnancy should follow the meal limit advice currently in place for PCBs, which will also be protective for PBDEs and lead. [emphasis added]

6.12. Fish Tissue Data

By way of introduction, the 2007 ATSDR/WDOH Health Consultation presented a historical review of earlier fish advisories in which it notes PCBs were the primary health concern when eating unlimited amounts of fish:⁵

The 1999 fish consumption advisory was later updated in March 2001 due to elevated PCB concentrations in Spokane River fish. The 2001 fish advisory based on a DOH report advised fishing enthusiasts that PCB concentrations in Spokane River fish were of concern. DOH concluded that exposure to PCBs through ingestion of Spokane River fish caught between the Washington/Idaho border and Ninemile Dam represented a public health hazard for persons who consumed fish from this area. In July 2003, SRHD and DOH issued a fish advisory which recommends against any consumption of fish between the Idaho border and Upriver Dam. For the reach between Upriver Dam and Ninemile Dam, DOH advised against eating more than one meal per month of any species. Although fish downstream of Ninemile dam contained some PCBs, levels were lower relative to upstream portions, thus fish was safe to eat. Cleaning and preparation to reduce exposure to some contaminants was advised.

New sampling and analysis data became available in 2005, allowing a more robust health analysis based on more recent measured PCB tissue concentrations, which now included sections of the Spokane River not previously sampled.

The determination of total PCBs based on Aroclor analysis in the 2007 Health Consultation relied on a more robust analytical procedure than did earlier fish advisories. The analytical method was still based on

Aroclor analysis, but many more Aroclor mixtures were included in the 2007 analysis. ATSDR/WDOH note that numerous Aroclors were considered:

PCB Aroclors (i.e., Aroclors 1016, -1221, -1232, -1242, 1248, -1254, -1260, -1262, and 1268) were analyzed using dual column gas chromatography electron conductivity detector (GC-ECD) in all species. These methods are modifications of EPA SW-846 methods 3540, 3620, 3665, and 8082. Aroclor results were summed to derive total PCBs.

ATSDR/WDOH conducted a comparison of historical PCB data to the current (2005) dataset and concluded that fish tissue levels decreased for some—but not—all fish species. However, the Agencies highlighted the fact that this was due to remedial actions and not to natural attenuation (or weathering), indicating further actions to either remove PCB-contaminated sediments, reduce further PCB river loading, or both may likewise reduce the fish tissue concentrations:

Historical and current data for PCBs (1994, 1996, 1999, 2001, 2003, 2004, and 2005) indicate a decline in the PCB levels of Spokane River fish. However, this trend was not consistent for each species of fish at every location and is not considered a strong trend when results of recent sampling are considered. It appears that PCB levels from the Idaho border to Upriver Dam drop significantly with the recent sampling data. The decline in PCBs may be a direct result of Ecology initiatives to reduce point sources. To confirm this apparent trend, Ecology will continue to monitor the Spokane River before the existing fish advisory is revised.

ATSDR/WDOH presented a comparison of the 2001 and 2005 data, which does show some attenuated levels. (See Exhibit 16.) However, a side-by-side comparison could not be made for many fish species.

Exhibit 16. Comparison of 2005 PCB Data vs. 2001 PCB Sampling Data

Table 5. Comparison of 2005 PCB data vs. 2001 PCB sampling data, Spokane River, Washington.

New Calculations (Based on current data)				Old Guidance (Based on former data)			
Species	N^a	Mean PCB Conc. (ug/kg ww)	Meals/month	N^b	Mean PCB Conc. (ug/kg ww)	Meals/month	Health advisory recommendation
Lake Spokane (Upper and Lower Long Lake)							
Largescale sucker (whole)	6	290	1	NA [*]	311	1	Safe to Eat Fish
Largescale sucker (fillet)	NA	NA	NA	19	101	2	
Brown Trout (fillet)	1	130	1	NA	NA	NA	
Smallmouth Bass (fillet)	4	52	3	10	37	4	
Mountain Whitefish (fillet)	9	59	3	6	73	2	
Ninemile Dam to Upriver Dam							
Bridgelip Sucker (whole)	3	69	2	NA	NA	NA	Eat no more than 1 Meal of Any Kind of Fish
Rainbow Trout (fillet)	6	113	1	12	169	1	
Largescale Sucker (whole)	3	1,823	0	NA	NA	NA	
Largescale Sucker (fillet)	NA	NA	NA	10	169	1	
Mountain Whitefish (fillet)	6	186	1	10	491	0	
Upriver Dam to Idaho Border							
Rainbow Trout (fillet)	3	55	3	10	494†	0	Do not Eat Any Fish
Largescale Sucker (whole)	6	89	2	NA	NA	NA	
Largescale Sucker (fillet)	NA	NA	NA	10	125	1	

N = sample size
ww = Wet Weight
ug/kg = micrograms per kilograms
NA Not available
^a Composites of 4-5 individual fish each, except Long Lake mountain whitefish which were analyzed individually.
^b Whole body samples are composites of five fish, fillets are individual fish.
^{*} Whole body samples for Largescale sucker were analyzed from individual fish.
† Used the mean average between both means (880 and 108 ppb wet weight)

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Consultation. Evaluation of PCBs, PBDEs and Selected Metals in the Spokane River, Including Long Lake Spokane, Washington. August 28, 2007.⁵

In addition to Aroclor laboratory analysis, some fish samples were analyzed for all 209 PCBs. Thirteen separate PBDE congeners were also analyzed, as were cadmium (Cd), arsenic (As), Pb, and Hg:

A subset of samples was analyzed for all 209 congeners. The sum of these congeners represents the total amount of PCBs... PBDE congeners (i.e., BDE-47, -49, -66, -71, -99, -100, -138, -153, -154, -183, -184, 191, and -209) were analyzed using gas chromatography mass spectrometry (GC/MS) by EPA method 8270...Lead, cadmium, arsenic and zinc were analyzed by Inductively Coupled Plasma Mass Spectrometry (ICP/MS) EPA method 200.8.

Analysis of the four heavy metals in fish tissue provided information on more current levels for six reaches of the Spokane River:

In 2005, Ecology conducted a study to obtain up-to-date information on concentrations of PCBs, PBDEs, and selected metals (zinc, lead, cadmium, and arsenic) in several species of sport fish and bottom fish in the Spokane River. In 2005, Ecology sampled one to four fish species each from six reaches along the Spokane River: 1) Upper Long Lake, 2) Lower Long Lake, 3) Mission Park, 4) Ninemile Dam, 5) Plante Ferry, and 6) Idaho Stateline during August through November 2005.

Of the four metals, only Pb was deemed important, and concern regarding this element *only* pertained to whole-fish samples and only involving pregnant women and children less than 6 years of age. With one exception in which Pb was detected only 0.02 ppm higher than the detection limit of 0.1 ppm, Pb was not detected in any fish fillet sample. Furthermore, even whole-fish samples contained Pb concentrations < 5 ppm. (See 0.)

Exhibit 17. Summary of Lead Concentrations in Spokane River Fish

Table 3A. Summary of lead concentrations in Spokane River fish compared to subsistence consumption screening values. Spokane, Washington.

Location	Species	Tissue type	N *	C/I	Lead mg/kg, wet weight		Range	Subsistence CVs (mg/kg)	
					Mean	Max.		lower-end	higher-end
Plante Ferry	Rainbow Trout	Fillet	3	C	0.12	0.14	<0.10 – 0.14	0.07 ^a	0.27 ^b
Mission Park	Rainbow Trout	Fillet	3	C	<0.10	0.14	<0.10 – 0.14		
"	Mountain Whitefish	Fillet	3	C	<0.10	0.19	<0.10 – 0.19		
Ninemile	Rainbow Trout	Fillet	3	C	<0.10	0.26	<0.10 – 0.26		
"	Mountain Whitefish	Fillet	3	C	<0.10	<0.10	<0.10 (all)		
Upper Long Lake	Mountain Whitefish	Fillet	3	C	<0.10	<0.10	<0.10 (all)		
"	Brown Trout	Fillet	1	C	<0.10	--	--		
"	Smallmouth Bass	Fillet	1	C	<0.10	--	--		
Lower Long Lake	Mountain Whitefish	Fillet	6	I	<0.10	<0.10	<0.10 (all)		
"	Smallmouth Bass	Fillet	3	C	<0.10	<0.10	<0.10 (all)		
Stateline	Largescale Sucker	Whole	3	C	4.2	6.7	2.6 – 6.7		
Plante Ferry	Largescale Sucker	Whole	3	C	2.9	3.2	2.6 – 3.2		
Mission Park	Largescale Sucker	Whole	3	C	3.5	4.2	2.8 – 4.2		
Ninemile	Bridgelip Sucker	Whole	3	C	2.9	3.1	2.6 – 3.1		
Upper Long Lake	Largescale Sucker	Whole	3	C	0.80	1.2	0.6 – 1.2		
Lower Long Lake	Largescale Sucker	Whole	3	C	0.33	0.57	0.14 – 0.57		

N = sample size
mg/kg = milligrams per kilograms
C = composites
I = individuals
*Composites of 4-5 individual fish each, except Lower Long Lake mountain whitefish which were analyzed individually.
NA – Not available
BOLD Values exceed comparison value
^a assumes 50% of meat portion of diet is fish
^b assumes 12% of meat portion of diet is fish

Source: Washington State Department of Health under cooperative agreement with the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry. Health Consultation. Evaluation of PCBs, PBDEs and Selected Metals in the Spokane River, Including Long Lake Spokane, Washington. August 28, 2007.⁵

6.13. Spokane's Remediation Efforts Will Have a Great Impact on Protecting Human Health

6.13.1. Background

Spokane's activities to reduce the discharge of PCBs to the Spokane River will have a significant impact on protecting human health. This is because fish contaminated with PCBs represents important source of exposure to PCBs—particularly, the group of highly chlorinated PCBs that bioaccumulate in fish and that are considered the most dangerous because they are associated with cancer. This sections analyzes two facts: 1) The general public is exposed to PCBs primarily from contaminated food, and fish is the most highly PCB-contaminated food group; and 2) Studies that have analyzed PCB blood levels in the general public have consistently shown that the highest PCB blood levels are in people who have a diet rich in fish.

6.13.2. CDC Biomonitoring Data Show PCB Body Burdens in the General Public Are Associated with Eating PCB-Contaminated Fish

While the PCB levels have been continuously decreasing in the U.S. environment and food supply since they were banned, there is evidence that all Americans are still being exposed to ubiquitous environmental contamination. This evidence is based on the biomonitoring studies conducted by the by the CDC in NHANES. The NHANES is a bi-yearly analysis of the health of U.S. general population that scientists from many disciplines routinely rely on in public health investigations.

CDC summarizes the design of the NHANES as a monitoring program of the general population (<https://www.cdc.gov/nchs/nhanes/index.htm>):²⁰

This study is designed to assess the health and nutritional well-being of children and adults in the U.S. The NHANES program began in the early 1960s and has been conducted as a series of surveys focusing on different population groups or health topics. In 1999, the survey became a continuous program that has a changing focus on a variety of health and nutrition measurements to meet emerging needs. The survey examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 of which are visited each year.

In addition to basic health information, NHANES also includes a biomonitoring investigation to measure the amounts of toxic environmental compounds that are accumulating in Americans in order to investigate exposure to toxic environmental compounds. The biomonitoring data provide crucial information on contaminant body burden levels in the general public, which are used to determine whether they are increasing or decreasing, which, in turn, informs regulators (like USEPA) on whether enforcement action is necessary to control contaminant production and/or releases into the environment. Biomonitoring data are also used as a metric to determine whether past efforts to control environmental exposure were appropriate or successful in protecting against exposures. When biomonitoring information is coupled with information on the prevalence and incidence rates of illnesses and diseases, it is also a powerful tool for scientists to identify what contaminants may be associated with specific health outcomes. Finally, it is used to identify the most important environmental sources and routes of exposure to environmental pollutants in the general public, which are the major foci of the following sections.

Biomonitoring data provide the best and most direct information with which to assess what environmental contaminants Americans are being exposed to because they constitute the canary-in-the-coal mine warning for scientists that body burden levels may be reaching toxic levels. Because NHANES is a continuous study, increases in contaminant body burdens can be tracked from a toxicological or medical standpoint and may reveal that specific toxic effects may be due to increased body burden; without the NHANES biomonitoring data, these may have gone unnoticed.

CDC generates biomonitoring data by taking blood samples from the general public and measuring the blood levels in those they have identified as representative of the U.S. (noninstitutionalized, civilian) population. Importantly, CDC selects participants who are not exposed to a hazardous waste site or exposed to workplace contaminants. These biomarker data are published in the *National Report on Human Exposure to Environmental Chemicals (NER)* and are stratified by age group, gender, and race/ethnicity.²¹ The NHANES data as measured in blood samples represent total exposures from *all* sources in the environment and, as such, represent the cumulative daily dose. However, statistical analyses and comparisons of different groups can and are used to identify the predominant exposure routes and sources of contaminant exposure. Furthermore, because exposures to bioaccumulating compounds like PCBs are from the contaminated U.S. food supply, it is possible to focus on participants' eating habits and foods they eat on a regular basis to identify specific contaminated food products.

CDC summarizes its biomonitoring program as follows:²¹

About CDC's Biomonitoring Program

Using advanced laboratory science and innovative techniques, the Division of Laboratory Sciences' Biomonitoring Program in the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention (CDC) has been in the forefront of efforts to assess people's exposure to environmental chemicals.

CDC's highly trained laboratory scientists have built on more than three decades of experience in measuring chemicals directly in people's blood or urine, a process known as biomonitoring. Biomonitoring measurements are the most health-relevant assessments of exposure because they measure the amount of the chemical that actually gets into people from all environmental sources (e.g., air, soil, water, dust, or food) combined. With a few exceptions, it is the concentration of the chemical in people that provides the best exposure information to evaluate the potential for adverse health effects.

NHANES II (1976–1980) was the first report to present biomarkers of environmental chemical exposure based on measured blood lead levels on a relatively small number of contaminants. Currently, a total of 265 compounds are measured in the general population.

In its 2012 publication, *Exposure Science in the 21st Century: A Vision and a Strategy*, the NAS National Research Council highlights the importance of the NHANES biomonitoring studies for identifying key sources of environmental exposures that lead to increased body burdens of toxic compounds:²²

The increasing collection and evaluation of biomarkers of exposure and effect also is providing growing opportunities for exposure science. The Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) published the first National Human Exposure Report in 2001, which used a subset of its subjects to assess the US population's exposure to environmental chemicals on the basis of biomonitoring data. The reports have been updated with publications released in 2003, 2005, and 2009, and annual reports are expected. The NHANES data provide a unique and growing potential for evaluating source-exposure and exposure-disease relationships in a national population-based representative sample", and that biomarker data sets "will be essential for evaluating the efficacy of exposure reduction policies, and for prioritizing and assessing chemical risks.

One such study using the NHANES biomonitoring data to identify the major environmental source of PCBs was conducted by Xue et al. (2014) in which the researchers identified fish ingestion as the most important factor associated with elevated PCB body burdens.²³ The approach they took was to evaluate patterns of PCB exposure based on NHANES data and combined them with a "market basket" food analysis based on an USEPA dietary model:

Studies have shown that the US population continues to be exposed to polychlorinated biphenyls (PCBs), despite their ban more than three decades ago, but the reasons are not fully understood. The objectives of this paper are to characterize patterns of PCBs in blood by age, gender, and ethnicity, and identify major exposure factors. EPA's Stochastic Human Exposure and Dose Simulation (SHEDS)-dietary exposure model was applied, combining fish tissue PCB levels from a NYC Asian Market survey with National Health and Nutrition Examination Survey (NHANES) dietary consumption data, and then linked with blood biomarkers for the same NHANES study subjects.

What Xue et al. found was that ethnic groups having a very high fish consumption rate had the highest PCB blood levels. Most importantly, in the group aged 12–30 years—the group born after the PCB ban and when PCBs levels were decreasing—the blood PCB levels were strongly associated with dietary exposure to fish; the association was the strongest in this subgroup:

For the 12 to 30-year age group, the “Asian, Pacific Islander, Native American or multiracial” group had the highest values, with patterns fairly consistent with fish consumption and modeled PCB exposure patterns. We conclude that for younger people, patterns correspond to reduced environmental contamination over time, and are strongly associated with fish consumption and dietary exposures.

The major finding Xue et al. highlighted was that a high fish ingestion rate was a key factor in PCB elevated exposures and PCB blood levels:

Food and Fish Consumption Patterns and Dietary Exposures by Ethnicity and Age Group

Our analyses confirm that fish consumption is a key factor in PCBs exposure, and reveal new findings on ethnicity- and age-related patterns. Ethnicity-related fish consumption patterns were fairly consistent with fish dietary exposure levels for both age groups. For the younger age group, both the fish consumption and modeled exposure patterns matched reasonably well with the pattern and rankings of blood PCBs among the studied ethnicities.

In conclusion, Xue et al. showed that banning PCB production in 1977 had produced the desired effect of lowering blood levels in the general public, except among those Americans eating a diet high in fish tissue (like those who are eating fish from the Spokane River):²³

CONCLUSIONS: The reduction in total blood PCB concentrations in each NHANES age group over two survey periods (2001–2002 and 2003–2004) is evidence of the

effectiveness of the US control measures on PCB release and production. Currently, the major route of PCBs exposure is dietary via consumption of fish and other foods with that tend to bioaccumulate PCBs present in the environment. This is particularly evident in A/P/N/M populations. Analysis of food consumption explained the blood concentrations of PCBs for the younger (12 to r30 years) age group and the A/P/N/M ethnicity group within that younger subpopulation. Dietary ingestion, particularly via fish consumption, remains a major route of exposure to environmental PCBs for the general human population.

While Xue et al. focused on the general population, many studies have taken another approach and targeted sport fishermen (the group for which the WDOH fish advisories have been developed). These studied directly compared PCB body burdens in sport fishermen with those who do not eat fish or who infrequently eat a fish meal.

For example, He et al. (2001) investigated the link between sport fishermen eating fish caught in the Great Lakes (which is highly polluted with PCBs) and their serum blood levels to determine whether their PCB levels were evaluated:²⁴

We linked data from three mixed cross-sectional/longitudinal surveys of Michigan anglers conducted by the Michigan Department of Public Health in 1973-1974, 1979-1982, and 1989-1993 to examine the association between sport-caught fish consumption and serum PCBs.

When He et al. evaluated the fishermen's levels in the context of the overall PCB body burden levels that had been decreasing in the general population over specific time periods, the sport fishermen had Aroclor levels two to three times higher than those in the general public who did not eat fish. Furthermore, the levels of PCBs actually increased in sport fishermen:

Serum Aroclor 1260 levels were 2-3 times higher in fish-eaters than in nonfish-eaters in all three surveys in both men and women. In nonfish-eaters, serum PCB levels rose between 1973-1974 and 1979-1982 [adjusted change) 0.30 log(ppb), p) 0.01] and then declined between 1979-1982 and 1989-1993 [adjusted change) -0.16 log(ppb), p) 0.002]. Among fish-eaters, serum PCB levels also rose between 1973-1974 and 1979-1982 [adjusted change) 0.45 log(ppb), p < 0.001] but were unchanged between 1979-1982 and 1989-1993 [adjusted change) -0.09 log(ppb), p) 0.14].

He et al. summarized their findings:

Predictors of serum PCB levels included annual fish consumption, gender, and age. We conclude that background human serum levels of Aroclor 1260 had declined by 1989- 1993 from earlier peak levels. Among consumers of sportcaught Great Lake fish, serum PCB levels did not significantly decrease, probably due to continued exposure and the long half-life of PCB.

These results have implications for the Spokane sport or recreational fishermen because it is likely that their blood levels were significantly increased due to eating unrestricted fish meals *before* the WDOH fish advisories were issued. Those body burden PCB levels have likely been significantly reduced by not only WHOD—who issued fish consumption advisories (which likely reduced consumption of PCB-contaminated fish) but also to Spokane’s remediation efforts that have reduced PCB contaminant loading in the river. It should be noted that the body burdens of those who ate Spokane PCB-contaminated fish prior to those mitigating efforts are likely still elevated because, as noted by He et al., it can take a long time (decades) to eliminate PCBs from the body. The additional PCB exposures *after* the fish advisories were put into place and Spokane began its remediation efforts would now be acting in concert to reduce the lower but continuous PCB exposures (assuming fishermen and their families do not exceed the number of meals of PCB-contaminated fish recommended by the fish advisories).

Other studies have focused specifically on the group of Americans who have the highest PCB body burden in the general public to identify why those individuals still have very high levels of PCBs in their bodies even though the levels in the general population have been decreasing. These studies show that other forces that are not often considered by scientists or governmental regulators may be the cause. These factors appear to be income levels and/or race.

Weintraub and Birnbaum (2008) showed there is racial disparity in PCB levels that is associated with those who eat certain types of fish.²⁵ In their study, Weintraub and Birnbaum singled out non-Hispanic Black fishermen who were eating whole catfish and found that this subgroup had some of the highest PCB body burdens—far greater than the those of the average American. They state that, while the NHANES studies have shown a continuous decline over the years, this lower-income group had the highest levels in the general population because they fish to support their diets with inexpensive locally caught fish and often eat whole fish, rather than preparing the fish consistent with the fish consumption advisories:

The human body burden of polychlorinated biphenyls (PCBs) sharply declined after production was banned in the US in 1979. For the 10% of the US population that remains most exposed to PCBs, fish consumption is the primary source. National Health

and Nutrition Examination Survey (NHANES) data indicates that the highest remaining PCB levels exist in a non-Hispanic black subpopulation. Our review suggests that catfish consumption may be a significant PCB source for the one million non-Hispanic black anglers who fish for catfish. In comparison to non-Hispanic white anglers, non-Hispanic black anglers consume more catfish, are more likely to eat the whole fish rather than just the fillets that contain less PCBs, and are more likely to fish in watersheds with high PCB contamination.

The researchers identify “racial disparities” as one of the most important contributors to the high PCB body burden group found in 10% of the population:

The primary source of PCBs for the 10% of the US population currently most exposed to PCBs are fish high on the food chain consumed from PCB-contaminated lakes, streams, and estuaries (Judd et al., 2004). This represents a significant shift from studies in the 1960s through 1980s that often attributed the highest PCB body burdens in humans to occupational exposure. As summarized in Table 1 and Fig. 1, the higher PCB levels in US populations during that era were found in completely or predominantly non-Hispanic black populations (Finklea et al., 1972; James et al., 2002; Krieger et al., 1994; Lordo et al., 1996; Robinson et al., 1990; United States Environmental Protection Agency (USEPA), 1980; Gray et al., 2005; Kutz et al., 1991; National Research Council, 1991). National Health and Nutrition Examination Survey (NHANES) data suggest such racial disparities persist...Economic status also likely contributes to disparities in PCB exposure. The rate of poverty remains elevated in the non-Hispanic black population and supports the persistence of subsistence fishing (DeNavas-Walt et al., 2006; Brown and Toth, 2001).

Lack of education and the inability to process complex information about the toxicity of chemical contaminants presented in fish advisories may make the recommendations useless because they are ignored:

To be effective, fish advisories must overcome these demographic, geographic, economic, and cultural forces to eliminate potentially high PCB exposure in the non-Hispanic black subsistence angler population. Fish advisories may not be meeting the challenge. It is unlikely subsistence anglers seek fish advisory information from a website upon which a state relies to disseminate advisories (Webber, 2006). Advisories may not respond to angler needs or, as a river flows through various jurisdictions, present different recommendations despite constant contamination (Campbell et al., 2002; Beehler et al., 2001; Burger, 2004; McDermott et al., 2003; Knuth et al., 2003; Chess et al., 2005). Such confusing and inaccessible guidance helps to explain why the non-Hispanic black

population in the Northeast US and urban areas are more likely to be restrained from fishing due to general water pollution concerns rather than specific fish advisories (Burger and Waishwell, 2001).

This finding is important to the current litigation. When evaluating or judging the appropriateness of Spokane efforts to reduce PCB loading into the river, it must be taken into consideration that lower-income groups who may be fishing the Spokane River might not follow the fish consumption advisories due to their economic situations. The only way to protect that segment of the population is by *physically preventing* PCBs from loading into the river and contaminating the fish (which is the goal of Spokane's remediation efforts).

While Weintraub and Birnbaum focused only on the factors that were most associated with lower-income groups eating catfish, in my experience it extends to lower income groups eating other species of fish; the Weintraub and Birman conclusions may be extended and applicable to this litigation. It should be noted that carp was added to the fish advisory in 2017 for Long Lake (McBride 2018), and other bottom feeders that bioaccumulate great amounts of PCBs—namely, largescale suckers—have been shown to have the highest levels of PCBs.²⁶

It should also be noted that certain ethnic communities around Spokane – including Russian and Laotian communities – regularly use the Spokane River as a food source and are therefore especially at risk. (Spokane Regional Health District; 1998 Fish Consumption Survey, Spokane River, Washington)²⁷.

One last point that needs to be stressed is that the Spokane fish advisories apply to sport fishermen and do not take into account the exposures to their family members, who could include pregnant wives, women of child-bearing age, and children. These groups are particularly sensitive to PCB exposures. My professional experiences have shown that those who fish to (inexpensively) supplement their diets provide meals for their entire families.

6.14. Spokane's Remediation Efforts Have and Will Continue to Reduce PCB-Fish Contamination and Associated Health Risk

6.14.1. Modeled Future Fish Concentrations Show Spokane Is Reducing PCB-Fish Tissue and Health Risks

The PCB levels in fish have been declining due to the city of Spokane's past remediation efforts to prevent PCB loading of the Spokane River. That remediation continues today and will into the future.

Both the cancer risk and noncancer health quotient (HQ) are proportional to the fish tissue PCB concentration. For example, a 10% reduction in the concentration will result in a 10% reduction in cancer risk and HQ.

The following dose and risk equations were used to calculate cancer risk and HQ for recreational fisherman eating PCB-contaminated fish are as follows:

Noncarcinogenic HQ: $HQ = \text{Dose}_{\text{noncancer}} \div \text{Reference Dose (RfD)}$

Cancer Risk: $\text{Cancer Risk} = \text{Dose}_{\text{cancer}} \times \text{Cancer Slope Factor (CSF)}$

The equations for calculating the fish tissue daily dose are as follows:

Noncarcinogenic Daily Dose:

$\text{Dose}_{\text{noncancer}} (\text{mg/kg-day}) = (C \times CF_1 \times IR \times CF_2 \times EF \times ED) \div (BW \times AT_{\text{noncancer}})$

Carcinogenic Daily Dose:

$\text{Dose}_{\text{cancer}} (\text{mg/kg-day}) = (C \times CF_1 \times IR \times CF_2 \times EF \times ED) \div (BW \times AT_{\text{cancer}})$

The exposure parameters and values used to calculate the daily fish tissue PCB dose are presented in Exhibit 18.

Exhibit 18. Exposure Assumptions

Parameter	Value	Unit	Comments
Concentration (C)	Fish Tissue	ug/kg	Mean Fish Tissue Concentration
Conversion Factor (CF ₁)	0.001	mg/ug	Converts contaminant concentration from micrograms (μg) to milligrams (mg)
Ingestion Rate (IR)	42 g/day	g/kg/day	Average recreational anglers (42 g/day)
Conversion Factor ₂ (CF ₁)	0.001	mg/ug	Converts contaminant concentration from micrograms (μg) to milligrams (mg)
Conversion Factor ₂ (CF ₂)	0.001	kg/g	Converts mass of fish from grams (g) to kilograms (kg)
Exposure Frequency (EF)	365	days/year	Assumes daily exposure consistent with units of IR given in g/day
Exposure Duration (ED)	30	years	Number of years eating fish
Averaging Time <i>noncancer</i> (AT)	10950	days	30 years
Averaging Time <i>cancer</i> (AT)	25550	days	70 years
Reference Dose (RfD)	2E-5	mg/kg/day	USEPA
Cancer Slope Factor (CSF)	2	mg/kg/day ⁻¹	USEPA

As discussed, reducing fish tissue PCB contaminant levels is the best and most cost-effective approach for mitigating PCB exposure to lower health risks in the general public because it targets fish contamination, which poses the greatest threat to human health. As noted above, the health risks are proportional to the fish tissue PCB concentrations, which are declining in the Spokane River as intended because of Spokane's remediation efforts.

6.14.2. Comparing PCB Loading from Spokane Remediation to No Remediation: Past, Current, and Future Scenarios

To evaluate the positive impacts the Spokane remediation efforts have produced in the past and will continue produce in the future, Dr. Gobas has carried out mathematical environmental modeling to specifically quantify the fish tissue PCB levels (as a percent reduction) that will result from Spokane's remediation. Dr. Gobas used the transport model to predict the *differences* in fish tissue PCB

concentrations at specific points in the Spokane River. The predictions were conducted under different scenarios assuming Spokane improvements are implemented versus no remediation has or will occur (i.e., remediation or no remediation). These comparisons illustrate the significant improvements that Spokane has already made—and will continue to make in the future—in protecting public health. As I previously discussed, fish consumption advisories are simple recommendations that communicate the risks from eating too many PCB-contaminated fish; these advisories are often intentionally or unintentionally ignored by some in the community, despite the good intentions of WDOH. In my experience, Spokane is implementing the only reasonable, practical, and available option to ensure public health will be protected. By preventing PCB loading into the Spokane River, the fish tissue levels of PCBs will be reduced, which will in turn have a significant role in reducing cancer risk and noncancer hazards because ingesting PCB-contaminated fish is the single-greatest source of exposure to humans today. While PCB contamination has slowly been decreasing in other environmental media, consumption of PCB-contaminated fish remains the most significant public health threat to the general population, and ingestion of PCB-contaminated fish is responsible for the highest PCB levels in the general population, according to NHANES.²⁰

In the following sections, I present the results of a fate and transport model that was conducted by Dr. Gobas to quantify reductions in PCB contamination of fish for specific sections of the Spokane River that are similar to transects used to develop the fish consumption advisories. Dr. Gobas has used his model to highlight the PCB reductions that are a direct result of Spokane's remediation activities. His modeling results show that significant improvements have already been made in protecting public health by reducing risk, and they also—importantly—show that Spokane's remediation efforts will continue to result in significant decreases in cancer risk and illness if they continue on the same course. It should be stressed that the length of time necessary for PCB levels in fish to drop to *acceptable* levels without remediation would be much longer (many decades) than the levels resulting from the active preventative removal efforts being undertaken by Spokane. The following sections summarize the percent reductions in fish tissue PCB levels based on Spokane's actively remediating PCBs versus the city doing nothing and simply relying on the WDOW fish consumption recommendations to protect the public.

Exhibit 19 shows the percent reductions resulting from Spokane remediation activities to reduce PCB loading from baseline (defined as the time period from 2001–2005) to current levels as of 2018. It shows that Spokane's remediation activities reduced concentrations of PCBs in fish by between approximately 7.1% and 12.1% at the following River stretches: Upriver Dam to Nine Mile Dam, Long Lake, and Little Falls Dam to Long Lake. This means that Spokane's remediation activities since the 2001-2005 time

frame reduced PCB body burdens, cancer risk, and HQ associated with eating PCB-containing fish from those stretches by approximately 7.1-12%.

Comparatively, had Spokane performed remediation activities between the baseline period to 2012, but not between 2012 and 2018, Spokane would have only reduced risk by between 5.8% and 9.4% at the same stretches. This shows that Spokane's actions during the 2012-2018 period reduced PCB levels in fish tissue by up to 3%, thus reducing PCB body burdens, cancer risk, and HQ by about 1–3%.

Exhibit 19. Comparing Spokane Remediation to No Remediation: Percent Reductions from Baseline (2001–2005) to Current (2018)

Change in Loadings:	Baseline to Current (2018)		Baseline to Current (2018)	
	Scenario: Observed with City of Spokane Reductions to 2018		Hypothetical if <i>no</i> City of Spokane Reductions after 2012	
Time Period:	2018	2018	2018	2018
	Scenario 1	Scenario 2	Scenario 1	Scenario 2
	Lower bound loads	Upper bound loads	Lower bound loads	Upper bound loads
River Stretch				
Above Monroe	-1.9%	-1.4%	-2.1%	-1.5%
Above Ninemile	12.1%	7.6%	9.4%	6.2%
Lake Spokane	12.1%	7.1%	9.4%	5.8%
Above Little Falls	12.1%	7.1%	9.4%	5.8%

Source: Frank Gobas Expert Report – Risk Assessment Worksheet

Exhibit 21 shows the modeled PCB tissue levels from baseline (2001–2005) to the projected levels in 2030, which show a marked reduction if Spokane continues its efforts for the next 12 years as proposed by Michael Baker International's expert report. Overall, if Spokane continues its efforts in line with MBI's recommendations, Spokane will have had decreased PCB concentrations in fish by between 11-17% (not including the stretch above Monroe) by 2030 compared to the 2001-2005 period. This means, by 2030, Spokane's remedial activities will have had reduced PCB body burdens, cancer risk, and HQ by about 11-17%.

Exhibit 20. *Cumulative PCB Reductions Resulting from Planned Spokane Improvements, 2012–2030*

2012 to Future (2030) - Cumulative Reductions Cumulative Loadings Reductions 2012 to Future based on Planned City of Spokane Improvements	
2030 Maximum 2018 Sc 1 + 2030 Sc 1	2030 Minimum 2018 Sc 2 + 2030 Sc 6
1.5%	0.9%
9.0%	5.9%
8.9%	5.5%
8.9%	5.5%

Source: Frank Gobas Expert Report – Risk Assessment Worksheet

In another PCB modeling series (**Error! Reference source not found.** and Exhibit 22), Dr. Gobas examines the combined reduction of PCBs in fish tissue that can be attributed to the City of Spokane’s activities between 2012-2018 and MBI’s proposed future remedial activities. Dr. Gobas shows that such activities would reduce PCB levels in fish tissue by between 5.5% and 9%. This means that, between 2012 and 2030, Spokane will have reduced PCB body burdens, cancer risk, and HQ by about 5.5-9%. This will produce a significant reduction in PCB body burden in just an 18-year period and, accordingly, protect public health.

Exhibit 21. Reductions from Planned Spokane Improvements

2012 to Future Future Planned City of Spokane Improvements (2030)					
2030 Scenario 1 Highest Spokane Treatment; Lower Bound Loads Other Sources	2030 Scenario 2 Highest Spokane Treatment; Upper Bound Loads Other Sources	2030 Scenario 3 Mid-level Spokane Treatment; Lower Bound Loads Other Sources	2030 Scenario 4 Mid-level Spokane Treatment; Upper Bound Loads Other Sources	2030 Scenario 5 Lowest Spokane Treatment; Lower Bound Loads Other Sources	2030 Scenario 6 Lowest Spokane Treatment; Upper Bound Loads Other Sources
-0.7%	-0.7%	-0.7%	-0.7%	-0.7%	-0.7%
7.2%	4.5%	7.2%	4.5%	7.2%	4.5%
7.2%	4.2%	7.1%	4.2%	7.1%	4.2%
7.2%	4.2%	7.1%	4.2%	7.1%	4.2%

Source: Frank Gobas Expert Report – Risk Assessment Worksheet

From between 2012 and 2018, Spokane's remedial activities will have reduced PCB loading in fish tissue by about 1.4-3.1%. Accordingly, Spokane's remedial activities reduced PCB body burdens, cancer risk, and non-cancer hazard quotient by about 1.4-3.1%. (Exhibit 23).

Exhibit 22. Reductions from 2012 to 2018

Change in Loadings: 2012 to Current (2018)				2012 to Current (2018)	
Scenario: Observed with City of Spokane Reductions to 2018				Hypothetical if <i>no</i> City of Spokane Reductions after 2012	
Time Period: 2018		2018		2018	2018
		Scenario 1	Scenario 2	Scenario 1	Scenario 2
		Lower bound loads	Upper bound loads	Lower bound loads	Upper bound loads
River Stretch					
Above Monroe		-2.0%	-1.5%	-2.2%	-1.6%
Above Ninemile		1.3%	0.1%	-1.8%	-1.4%
Lake Spokane		1.3%	0.1%	-1.8%	-1.3%
Above Little Falls		1.3%	0.1%	-1.8%	-1.3%

In summary, the current cancer risk levels calculated by ATSDR and WDOH from eating Spokane fish contaminated with PCBs are 10–100 times the *de minimis* risk level. All of the Spokane remediation efforts described above will not only improve the general health of the Spokane River but will reduce the PCB body burdens of people who eat Spokane fish by lowering the fish tissue PCB levels. Lowering the fish tissue PCB levels will result in a direct and proportional reduction in the cancer risk, which is currently very high, and it will also serve to reduce illness and disease.

Since the fish tissue PCB levels are directly proportional to the cancer risk and noncancer health hazards, Spokane's efforts have already reduced the health threats from PCBs and will continue to do so in the future. With continued remediation into the future, it is logical to assume that Spokane's efforts will also decrease the time necessary for the Spokane River to ultimately fully recover from PCB pollution that has accumulated over many decades.

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In the United States District Court Eastern District of Washington

City of Spokane v. Monsanto Co.

Expert Rebuttal Report of

Richard L. DeGrandchamp, PhD

December 17, 2019

A handwritten signature in black ink that reads "Richard DeGrandchamp". The signature is written in a cursive style and is positioned above a horizontal line.

Richard L. DeGrandchamp, PhD

President and Principal Toxicologist

Scientia Veritas, L.L.P.

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1. REBUTTAL COMMENTS: DRS. KEENAN AND EATON

This rebuttal report focuses primarily on the opinions expressed in the expert reports of Drs. Keenan and Eaton.¹ Both have expressed opinions on whether the Spokane polychlorinated biphenyl (PCB)-contaminated fish pose a threat to the public based on human health risk assessments. My rebuttal responses address both the risk assessment methodology they used to support their conclusions that PCBs do not pose either a noncancer health hazard or cancer risk, as well as their conclusions.

1.1. Rebuttal Responses to Dr. Keenan's Opinion

1.2. Dr. Keenan Does Not Use the U.S. EPA or DOH Standard Protocol for Evaluating Fish Risk

My general rebuttal opinion for Dr. Keenan's analysis of PCB-related health is that he relies on a risk assessment approach that is neither appropriate nor necessary to specifically address the public health threat posed by PCBs.

I have conducted approximately 100 Human Risk Assessments for PCB-contaminated sites and have also assisted or been technically involved with seven state departments of health (and the Agency for Toxic Substances and Disease Registry [ATSDR]) to assist them in choosing the best toxicological approach and methods that would yield the best and most-detailed results. In these efforts, I have always recommended following the most scientifically tenable approach that introduces the least amount of uncertainty and would provide credible results.

As I discussed in Volume 3 of my expert report, while the U.S. Environmental Protection Agency (EPA) is the environmental regulatory agency charged with enforcing remediation according to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); and other

¹ I also addresses certain points made by Dr. Desvousges and Mr. Herman, as noted throughout.

statutes, it does not typically oversee or engage directly in matters relating to developing fish advisories specifically for protecting the public with detailed recommendations for fish consumption. Those types of analyses are typically performed by ATSDR (which is the only Agency that is specifically charged by Congress to protect public health). If requested by states, ATSDR collaborates with the state health department to conduct a Health Consultation in which the health threats posed by eating contaminated fish are evaluated and a fish consumption advisory is formulated.

The distinctions between the types of health studies performed by U.S. EPA as opposed to those conducted by ATSDR and state health departments are very important. The scientific methodologies used by the two groups are very different because the goals are different, and the results and conclusions are used for different purposes. Dr. Keenan's opinion relies on the probabilistic U.S. EPA Human Health Risk Assessment (HHRA) methodology he used to conclude that PCB-contaminated fish do not pose a significant health threat to Spokane fish consumers. While I will provide some critiques of the specific assumption his HHRA is based on, my rebuttal opinion is that he simply used the wrong scientific approach. While the issues in this case focus on the health threats from eating contaminated fish, his approach is best suited to a U.S. EPA-type investigation in which there is only one issue that needs to be addressed: does the contaminated site pose unacceptable risk or not? Answering this single question is the sole goal of an HHRA for a U.S. EPA site where the goal is to decide whether remediation needs to be enforced or not. The Spokane River is not a U.S. Superfund site; therefore, an HHRA is an inappropriate methodology to apply in this case. Essentially Dr. Keenan has come to *one* conclusion: the fish tissue levels of PCBs do not pose a significant human health risk (i.e., the risks are acceptable). I have already discussed the issue of what is an acceptable risk level in Volume 3 of my report. The standard Dr. Keenan relies on is, once again, a U.S. EPA standard that was developed specifically to determine whether or not U.S. EPA has reasonable scientific justification for enforcing remediation. What he fails to acknowledge is that an HHRA is used to support a U.S. EPA decision, and the acceptable risk level framework he is basing his conclusions on is not appropriate for this case. U.S. EPA's acceptable risk framework is based on many factors, including cost and the practicality of remediation.. The acceptable risk framework is not relevant to this case. Dr. Keenan's HHRA conclusions stand in stark contrast to those of Washington State Department of Health (DOH) experts, triggering the hypothetical question: *"If Dr. Keenan is correct and PCB-contaminated fish tissue really do not pose an unacceptable risk, then the DOH Fish Consumption Advisories are not justified and should be considered unnecessary and stopped."* In other words, both DOH and Dr. Keenan cannot be correct regarding the threat posed by eating PCB-contaminated fish; one must be incorrect.

My opinion is that Dr. Keenan has used an inappropriate methodology to evaluate the health threat posed by eating PCB-contaminated fish and that the protocols developed over the last decade and implemented by DOH constitute the appropriate method for evaluating health threats and making public health recommendations to protect the public, as DOH is charged to do. While the U.S. EPA HHRA methodology Dr. Keenan has used to support his opinion is a generally accepted approach for U.S. EPA sites, where only one single calculated risk estimate is needed to justify determination of whether or not to remediate, river cleanup to remove PCBs from the sediments is not an issue here.

Dr. Keenan's conclusions appear to primarily pertain to the average sport fisherman. He ignores the possibility that the fish consumption surveys could be biased because he does not take into account fish consumers who may be ignored. This would include those who live in poverty or may not want to "get involved" with regulatory authorities. Nevertheless, Dr. Keenan accepts the survey information as fact.

DOH is the lead state agency charged with protecting the entire Spokane fish consumer population. DOH is following and providing detailed information to the public about what types of fish are safe to eat and in what quantities (i.e., per month).

In applying his HHRA methodology to determine whether PCB-contaminated fish pose an unacceptable risk, Dr. Keenan relied on a mathematical "simulation" with numerous hypothetical populations and assumptions about PCB exposures. While he supports these hypothetical assumptions with studies, it is important to know the strengths and weaknesses of the studies themselves because of how he defines the hypothetical assumptions and what population he is representing in his HHRA. For example, while Dr. Keenan makes assumptions about the fish ingestion rate, it is important to define the population that his ingestion rate represents. Indeed, defining the ingestion rate is perhaps the single-most important assumption in any HHRA. In my experience as an U.S. EPA consultant and expert witness, the fish consumption ingestion rate is the most important assumption in an HHRA because it is the focus of heated disagreement and arguments both in court and in negotiating a remedy for U.S. EPA lead remedial investigations. What is lost in many of these disagreements is that the "true" fish consumption rate can never be verified because there is a great deal of uncertainty in data gathered in fish consumption surveys, which is widely recognized in the field of toxicology. DOH has conducted numerous fish consumption surveys and has candidly admitted to and pointed out areas of uncertainty (which I discuss below). The importance of this single fish consumption assumption cannot be overstated as it is literally the key assumption that—for many contaminated rivers—governs whether the risks calculated in an HHRA are acceptable or unacceptable. I have never encountered a state health department that has used the type of

probabilistic HHRA Dr. Keenan used to evaluate the health risks from fish ingestion for the purpose of protecting the public. Nor to my knowledge has it been used to develop fish consumption advisories.

To avoid the numerous hypothetical assumptions necessary when conducting a complex HHRA, most state health departments follow a much more simplified and scientifically tenable risk assessment approach. This is the approach that all states, including Washington State DOH, follow because it is far superior and more direct in evaluating whether specific species from different rivers are safe to eat and, if not, how many fish can be eaten without toxic effects being manifest. The reason the DOH risk evaluation is so superior is that it does not rely on hypothetical simulations, fish consumption rates, or other assumptions that cannot be verified.

The scientific methodology used by DOH to develop fish advisories for PCB-contaminated fish is simply based the “safe” daily intake of PCBs; it is unnecessary to calculate the site-specific fish consumption rates because they do not need to be considered. In fact, the DOH scientific approach is elegant in its simplicity, and the only data needed to evaluate the health threat posed by PCBs is the safe dose, or reference dose (RfD), and the fish tissue PCB concentrations. With this approach, there is no need to dispute the assumed site-specific fish consumption rates nor any other hypothetical scenario. I explain this scientific method in detail in Section 1.3 and provide a simple analogy.

Finally, it should be noted that even U.S. EPA uses the same equations and methodology as DOH when it evaluates the risk from eating contaminated fish (this is general guidance). In fact, U.S. EPA developed the fish risk assessment methodology DOH uses, as stated by the Washington Department of Ecology (DOE): [1]

DOH uses an approach similar to that in EPA’s Guidance for Assessing Chemical Contaminant Data for use in Fish Advisories Vol. 1-4 for assessing mercury, PCBs, and other contaminants (EPA, 2000). These guidance documents provide a framework from which states can evaluate fish tissue data to develop fish consumption advisories, based on sound science and established procedures in risk assessment, risk management, and risk communication. [1]

The referenced document is one I have relied on for many years for fish risk assessments because it was specifically developed for state health departments whose mandate is to protect the general public of their states. U.S. EPA’s Executive Summary states the overarching goal of its fish risk assessment guidance, which is to provide “state, local, tribal, and federal agencies” with a “standardized” risk assessment methodology for fish ingestion: [2]

State, local, tribal, and federal agencies currently use various methods to estimate

risks to human health from the consumption of chemically contaminated, noncommercially caught fish and shellfish. A 1988 survey, funded by the U.S. Environmental Protection Agency (EPA) and conducted by the American Fisheries Society, identified the need for standardizing the approaches to evaluating risks and developing fish consumption advisories that are comparable across different jurisdictions. Four key components were identified as critical to the development of a consistent risk-based approach: standardized practices for sampling and analyzing fish, standardized risk assessment methods, standardized procedures for making risk management decisions, and standardized approaches to risk communication.

To address concerns raised by the survey respondents, EPA has developed a series of four documents designed to provide guidance to state, local, tribal, and regional environmental health officials responsible for issuing fish consumption advisories. [2]

Dr. Keenan's HHRA is not a standard approach, nor am I aware of any state health department that uses a probabilistic HHRA to protect the public for any type of health evaluation including fish consumption advisories.

That is, the underlying basis for fish consumption advisories is to issue alerts and warnings about contaminated fish and that is *solely* based on the RfD, which requires no information about fish consumption rates. For example, to alert the public about eating contaminated fish U.S. EPA often issues alerts about the health risks as a public service and not to support remediation. For example, it has prepared a detailed risk analysis for fish contaminated with mercury (Hg), which is a nationwide contamination problem because Hg is an airborne contaminant that does not recognize state boundaries. Thus, it is important for every state health department to know how to conduct risk assessments and fish consumption advisories to protect the general public from the toxic effects from this ubiquitous contaminant.

To address the risks posed by eating fish contaminated with Hg, the U.S. EPA and the U.S. Food and Drug Administration (FDA) developed a detailed website, complete with numerous risk assessment guidance documents. [3] (See Exhibit 1.)

**Exhibit 1. U.S. EPA Risk Assessment for Fish Contaminated with Mercury
[3]**

EPA-FDA Fish Advice: Technical Information

This webpage contains detailed information on the underlying calculations for the fish advice for women of childbearing age (about 16-49 years old), pregnant and breastfeeding women, and parents and caregivers of young children. It contains the following information:

1. How the chart for FDA's and EPA's fish advice was derived.
2. Sortable table of fish species that contains data used in separating the fish into categories, such as mercury concentrations and the number of weekly servings.
3. Recommended portion sizes for children based on age.

The approach U.S. EPA and the FDA used to evaluate risks from eating Hg-contaminated fish was solely based on the RfD. As I stated above, it is not necessary to develop a fish ingestion rate with this approach, as the risk is based only on the safe daily intake as described in Exhibit 2.

Exhibit 2. U.S. EPA–FDA Relies Solely on the RfD for Fish Risk Assessments [3]

How FDA and EPA derived the categories in the fish chart

The agencies decided which category each fish belonged to by calculating the highest average amount of mercury that could be in a fish when eaten one, two, and three times a week without going over the maximum acceptable mercury intake amount for an average pregnant woman. The agencies determined the maximum acceptable intake amount by comparing the reference dose (RfD) developed by EPA to the predicted exposure from the consumption of different fish species. An RfD is determined to be a rate of exposure that a person can experience over a lifetime without appreciable risk of harm; however, the RfD for mercury is protective of neurodevelopmental effects from a critical window of development for a fetus during pregnancy. The RfD includes a 10-fold uncertainty factor to allow for variability among individuals and groups, including individuals who are not pregnant. By expressing the advice in terms of recommendations for weekly intake of fish based on the RfD, the agencies aim to help consumers reduce exposure to mercury, while also enabling them to achieve the health benefits from eating fish. We describe the equations and results for determining which fish we placed in each category below.

Exhibit 3 shows that the U.S. EPA–FDA scientific approach uses an equation similar to that used by DOH and that is solely based on the RfD. More importantly, it does not address the issue of a site-specific fish ingestion rate.

Exhibit 3. U.S. EPA–FDA Equations For Fish Risk Assessments [3]

Equations for determining which category each fish went in

The boundaries for each category (or screening values) were calculated using equation 5-4 from EPA's *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis Third Edition*

$$SV = \frac{RfD * BW}{CR}$$

where

SV = screening value for a noncarcinogen (µg/g)

RfD = reference dose (µg mercury/kg-d)

BW = body weight (kg)

CR = mean daily consumption rate of the species of interest (g/d)

For this fish advice, we used the screening value as the highest average amount of mercury in fish that would not exceed the reference dose at a given consumption rate. The consumption rate (CR) was calculated using the following equation:

$$\text{Daily consumption rate } \left(\frac{g}{d}\right) = \text{serving size } \left(\frac{oz}{\text{serving}}\right) * \frac{28.3 g}{oz} * \text{weekly servings } \left(\frac{\text{servings}}{wk}\right) * \frac{1 wk}{7 d}$$

It should be stressed that while a “fish ingestion rate” is one of the parameters listed in the EPA–FDA equation, this term is not the same as the *site-specific* fish ingestion rate Dr. Keenan used in his probabilistic risk assessment. Rather, the above refers to the minimum recommended fish consumption rate to promote a healthy diet that is recommended by U.S. EPA–FDA—8 to 12 ounces per week. That is, the fish ingestion rate is a dietary recommendation used to determine the number of fish meals that will protect pregnant women or women of childbearing age. [3]

1.3. DOH Fish Consumption Advisories

The current (2019) DOH Fish Consumption advisory is presented in Exhibit 4. This table shows that the number of recommended fish meals per month is species and location specific. DOH considers these meal rates to be protective; exceeding them could produce toxicity.

Exhibit 4. Current, 2019 DOH Fish Consumption Advisories [4]

Fish Species	Advisory	Contaminant	Location Description
Spokane Arm - Mouth upriver to Little Falls Dam			
Largescale Sucker	Up to 1 meal per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Brown Trout	Up to 4 meals per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Rainbow Trout	Up to 4 meals per month	PCBs, PBDEs, Mercury	Spokane Arm - Mouth upriver to Little Falls Dam
Little Falls Pool - Little Falls Dam to Long Lake Dam			
Largescale Sucker	Up to 4 meals per month	PCBs, PBDEs, Mercury	Little Falls Pool - Little Falls Dam to Long Lake Dam
Northern Pikeminnow	Up to 4 meals per month	PCBs, PBDEs, Mercury	Little Falls Pool - Little Falls Dam to Long Lake Dam
Long Lake (Lake Spokane)			
Largescale Sucker	Up to 1 meal per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Mountain Whitefish	Up to 2 meals per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Northern Pikeminnow	Up to 2 meals per month	-	Long Lake (Lake Spokane)
Rainbow Trout	Up to 4 meals per month	-	Long Lake (Lake Spokane)
Brown Trout	Up to 1 meal per month	PCBs, PBDEs, Lead	Long Lake (Lake Spokane)
Common Carp	Do not eat	PCBs	Long Lake (Lake Spokane)
Yellow Perch	Up to 8 meals per month (healthy choice)	-	Long Lake (Lake Spokane)
UpRiver Dam to Nine Mile Dam			
Largescale Sucker	Up to 2 meals per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Mountain Whitefish	Up to 1 meal per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Rainbow trout	Up to 2 meals per month	PCBs, PBDEs, Lead	UpRiver Dam to Nine Mile Dam
Idaho Border to Upriver Dam			
All Fish (Spokane River)	Catch and release only	PCBs, PBDEs, Lead	Idaho Border to Upriver Dam

I have conducted more than 100 HHRAs (and teach a Human Health Risk Assessment graduate-level course). I have also assisted many state health departments in developing fish consumption advisories (which have been based on the U.S. EPA fish risk assessment methodology [2] that DOH also follows). I have extensive knowledge of the two types of investigations and lecture on the strengths and weaknesses of these two types of health studies. My opinion is that the U.S. EPA/DOH methods are the best means with which to determine the level of fish that can be consumed safely.

While an HHRA is typically conducted for hazardous waste sites where U.S. EPA is the lead governmental agency, an HHRA does not provide any information on how much contaminated fish can be eaten by fish consumers in the general population or the risk from eating specific fish. It is very limited because it provides only a single combined risk assessment to simulate the “best estimate” risk for the assumed population. U.S. EPA typically conducts an HHRA to determine if remedial action should be taken to clean up hazardous contaminants in a river, and Dr. Keenan’s HHRA would be appropriate for that type of analysis. But his HHRA cannot be used to protect, inform, and warn the public about the health threat from specific species at different areas. As I discussed in Volume 3 of my report, ATSDR and State health agencies are responsible for protecting the public. U.S. EPA is responsible for enforcing cleanup. In other words, the sole purpose of an U.S. EPA HHRA is to determine if remediation is necessary and to provide technical support for any decisions made—particularly if those decisions or efforts are challenged in court. Simply put, an HHRA provides no health information to the public

regarding the safe level of fish consumption. In fact, I have extensive experience in my toxicology practice in which the HHRA results indicated there is no health threat, but a fish consumption analysis was necessary to prevent toxic effects. In this case, DOH's finding that fish consumption advisories are necessary to protect the public contradicts Dr. Keenan's conclusion that eating PCB-contaminated fish does not pose a health risk. In other words, there would never be a need for a fish advisory in cases where an HHRA concluded that eating contaminated fish did not pose a health risk. The fact that DOH has developed fish advisories supports my opinion that Dr. Keenan's HHRA is either wrong or is misleading, since both Dr. Keenan and DOH cannot both be correct. Dr. Keenan's conclusions seem to indicate Spokane fish consumers need no protection and that the fish consumption advisories are a waste of effort and time.

In contrast to Dr. Keenan's HHRA, the DOH Fish Consumption Advisories provide reasonable, actionable, and useful information that members of the public can use to protect their health. These are the fundamental reasons that health agencies rely solely on the safe daily exposure levels represented by the RfD rather than HHRAs (which are unnecessary). Put another way, if HHRAs provided verifiable health information, health agencies would be conducting them; after all, they have experts who routinely conduct both types of health evaluations. Those experts have concluded that—from a toxicological perspective—fish consumption advisories are the most scientifically tenable investigations. HHRAs are limited in that the risks described in HHRAs can never be verified as the “true” risks (e.g., the calculated risks can never be proven or substantiated by actual cancer incident rates). The mathematical models are built on numerous hypothetical scenarios. The following sections briefly highlight these two types of health assessments and provide some contrasting features. These points support my opinion that, in this case, the DOH Fish Consumption Advisories should be given deference, as they rely entirely on the RfD, or daily safe dose.

1. Fish Consumption Advisory: This type of health evaluation calculates the maximum number of PCB-contaminated fish that can be safely eaten before toxic effects could become manifest. That is, when fish consumers do not exceed the maximum number of fish meals presented in the DOH Fish Consumption Advisory, no PCB-related toxicity should occur. This type of toxicological analysis relies *only* on the “safe” daily intake of PCBs that has been well-established. The safe daily intake is represented by the single toxicity value—the RfD. Simply put, by relying only on the safe daily intake, the fish consumption advisories are not confounded by hypothetical assumptions. Most importantly, they do not rely on fish consumption surveys, which may be biased (due to the manner in which the survey is

conducted or scientific procedures used to aggregate the survey data), so are free of any hypotheticals that cannot be verified. For example, no information is necessary regarding fish ingestion rates for different individuals or different ethnic groups because the safe fish consumption rate is only governed by the RfD; it is this bright line that separates healthy fish consumption (consuming PCB-contaminated fish *below* the RfD) from fish consumption that can be toxic (eating PCB-contaminated fish in excess of the RfD). Because it is not necessary to assume what the fish ingestion rates are, fish advisories avoid contentious discussion on this issue. This is why state health departments, including DOH, rely solely on fish consumption advisories to protect the public rather than other types of health evaluations.

2. U.S. EPA HHRA: A risk assessment can also be conducted to estimate the health risks posed by eating PCB-contaminated fish. However, this type of risk assessment is typically conducted for enforcement action based on a single *hypothetical*, assumed fish consumer that is selected after the mathematical simulations to represent the population are complete.

Several DOH documents present the methodology for calculating the safe number of fish meals that can be eaten per month. All methods are based on the safe *daily* intake of PCBs, which is represented by EPA's RfD toxicity value of 0.00002 milligram/kilogram-day (mg/kg-day: the number of mg PCBs per kg body weight every day). In other words, as long as this daily PCB intake does not exceed the RfD, no significant toxic effects are expected. The fish consumption advisory simply allows toxicologists to determine the number of fish meals that can be eaten every month that will not exceed the RfD. EPA defines the RfD as:

Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. [5]

Although the toxicological method for deriving an RfD is a multistep process starting with identifying the dose that causes toxicity in animal studies (from peer-reviewed scientific journals) and adjusting to account for species differences (extrapolating from laboratory animals to humans), the concept is easily explained with the following simple analogy. Aspirin (acetylsalicylic acid) is an analgesic (pain reliever) that also reduces inflammation (swelling of tissue and joints) and has been used worldwide for more than a century. It is sold as an over-the-counter (OTC; no prescription necessary), nonsteroidal anti-inflammatory drug (NSAID). This means that while many people use it, they must self-medicate

themselves and take care not to take more aspirin than the recommended daily dose. Because it is an OTC drug that is not prescribed by a physician, it is important that an individual knows the safe daily dose before taking it that. This safety information is clearly listed on the label (along with cautionary contraindications for children and preexisting medical conditions). The label states that each aspirin tablet is 325 mg and that the maximum number of tablets that should be taken is 12 tablets per day (24-hour period) which means that the safe daily intake is 3,900 mg/day (i.e., 12 tablets x 325 g-per tablet = 3,900 mg). In other words, if a person takes 12 aspirins per day (or less), no toxic effects are expected (exceeding this safe dose level could produce toxic effects like vomiting, tinnitus, confusion, hyperthermia, rapid respiration, metabolic acidosis, and multiple organ failure). [6] In other words, the safe daily intake dose on the label is simply the RfD for aspirin; although the RfD is referred to as a *toxicity value*, it is actually the bright line that separates a safe dose (dose lower than the RfD) from the toxic dose (greater than the RfD). The RfD is the safe dose that should not be exceeded.

The toxicological approach used by the pharmaceutical company (i.e., aspirin manufacturer) to calculate the safe daily aspirin dose is the same methodology used by EPA to develop the RfD for PCBs.

It should be noted that I specifically use the term *safe* dose in this report to describe the maximum chemical dose that that is not expected to cause toxicity. This issue can be cleared up by noting that when the daily chemical dose is below the RfD it is a safe dose, but when the daily dose exceeds the RfD, toxic effects may be manifest. Therefore, the RfD serves as the point of departure. For example, when a person suffering from muscle aches or fever takes 12 aspirin tablets per day, the drug effect is efficacious to treat those symptoms, and no toxicity is expected. However, if that self-medicating person takes more than the recommend amount of 12 tablets per day (thinking more is better), that person may experience toxic or lethal effects (medically referred to as *salicylate poisoning*; starting with nausea and vomiting, which may progress to include cerebral edema and coma, and can ultimately lead to cardiopulmonary arrest). [7] Therefore, a safe daily dose is defined as ≤ 12 aspirins, and a toxic dose is more than that number.

It must also be stressed that the underlying *assumption* of a safe daily dose—as defined by the RfD—for any chemical is that a person is not being exposed to other sources of that chemical. This is an important assumption to highlight for both aspirin and PCBs. Prior or concurrent chemical exposures often produce body burdens (the amount typically measured in blood sample) that are already high and close to toxic levels. These exposures may be unintentionally ignored or not immediately recognized, which can have dire toxic consequences. For example, if a person suffering from the flu takes aspirin to reduce fever and relieve muscle aches, but that person is also on prescribed drugs containing aspirin, that person could be

unintentionally poisoned by not knowing the other drugs contain aspirin (there are more than 60 common OTC and prescribed drugs containing aspirin [8]). If blood levels of aspirin from other medications were already high, taking aspirin tablets could cause a medical crisis. That is because the toxicological concern is the total body burden (in a clinical setting, body burden is based on *total* aspirin exposure with mild to severe salicylate poisoning being a concentration of 40–100 mg/dL). If a person taking aspirin is not aware of aspirin contained in other drugs he or she is taking, the results could be catastrophic. The same is true for PCB exposures, but neither DOH nor Dr. Keenan considers the fact that *all* U.S. citizens already have an existing PCB body burden [9] that has nothing to do with eating Spokane fish; from a toxicological perspective, the DOH fish consumption rates may be too high for certain individuals.

While the RfD is interpreted as the safe daily dose in calculating the maximum number of fish that can be eaten, it does not take into consideration the fact that the general population already has a preexposure body burden (prior to eating any PCB-contaminated Spokane River fish). The PCB levels in the general population are carefully measured with blood samples every two years by the U.S. Centers for Disease Control and Prevention (CDC). [9] As in the aspirin example, ingesting any *additional* PCBs from Spokane fish will simply add to the body burdens of the fish consumers. Therefore, even when DOH calculates the number of fish that can safely be eaten, the number should be considerably lower to account for the already-elevated PCB levels in some Spokane fish consumers. As I discussed in Volume 3 of my report, people who maintain a diet rich in fish (from any source) have been shown to have the highest PCB body burdens in the general population, so the RfD may not be a safe exposure for this particular group (even when they do not exceed the maximum number of DOH-recommended fish meals). In that group, PCB levels could accumulate to toxic levels without their knowing it because people do not typically monitor their PCB levels. This could pose medical issues for both toxic systemic effects and for significantly increasing their risk for cancer. I stress this point not because I am suggesting that DOH should adopt an alternative risk assessment approach, rather that the DOH fish advisories could underestimate health risks for PCBs for some groups (that already have high PCB body burdens and who do not know it) and not be protective for the entire fish-eating population. My opinion rebuts Dr. Keenan's opinion that the fish consumption advisories are overly protective; he has not considered preexisting PCB body burdens in his analysis.

As shown with the simple analogy above, calculating the number of PCB-contaminated fish that can be safely consumed is straightforward, easily understood, and can be determined for any chemical (for which a safe daily intake—the RfD—has been determined). It *does not* include knowing any more than 1) the chemical-specific RfD, and 2) the fish tissue contaminant level. Most importantly, it does not include any

hypothetical assumptions about fish consumption rates for average and upper-bound fish eaters or need to account for differences between the frequency of fish meals for different ethnic groups or those who eat subsistence levels of fish meals. In contrast, Dr. Keenan's HHRA is completely governed by these hypothetical daily fish consumption rates. None of this information is necessary with the U.S. EPA/DOH approach because it is solely based on the safe daily PCB dose (i.e., RfD)

In this sense, the DOH approach is completely free of any hypothetical or extraneous information. As such, it can be regarded as a straightforward toxicological analysis. Just like the aspirin label provides the necessary cautionary warning that more than 12 tablets per day may produce toxic effects, the DOH Fish Consumption Advisory provides easily understood toxicity information that is scientifically tenable.

It is also important to note that even when both the risk assessment and fish advisory calculation are based on the same fish species and fish PCB contaminant levels, the results and conclusions of the two types of health evaluations are in stark contrast. Whereas the risk assessment may indicate eating PCB-contaminated fish poses no risk (to the *assumed* exposed population), the fish advisory puts restrictions on the number and types of fish that can be safely eaten. It is not clear from Dr. Keenan's HHRA results and conclusions that the current PCB levels do not pose unacceptable risk, if he has also concluded that no restrictions or recommendations need to be developed for eating Spokane PCB-contaminated fish and fish consumers can eat any fish *ad libitum*. It is my opinion that DOH's fish consumption advisories are necessary, reasonable, and appropriate (and may actually underestimate the noncancer health threat).

For the above reasons, I have primarily focused on the straightforward, scientifically tenable, and easily understood analysis that all toxicologists rely on: fish consumption advisories. This is because, described in its simplest terms, the fish consumption advisory sets a limit on how much PCB exposure is safe. Exceeding the number of recommended fish meals could have toxicological effects because safe PCB dose would be exceeded.

1.4. Dr. Keenan Critique: I Did Not Conduct an Independent Analysis of Current Health Risks

In Volume 3 of my expert report, I analyzed, reviewed, and summarized numerous ATSDR/DOH Health Consultations. I stated the purpose of that analysis, which was to evaluate the risk assessment methodology to determine if it was reasonable and scientifically tenable and also if it followed generally accepted toxicological practices. I concluded they did.

When I reviewed the ATSDR/DOH health consultations (pre-2012), they were consistent with many fish consumption advisories I have reviewed or participated in over the last couple of decades. When I evaluated the more recent DOH fish advisories [10] based on the 2012 DOH fish data, they followed the same procedures, and I concluded that DOH has continued to apply the same toxicological approach as the past evaluations and its findings and conclusions were correct.

In the following sections, I present a detailed analysis of the DOH fish advisory (using the 2012 DOH fish dataset) and apply the same methodologies and procedures detailed in the ATSDR/DOH consultations (post-2012). However, it should be noted that U.S. EPA/DOH fish risk assessment methodology has not changed over the last two decades, and it is not expected to undergo any changes in the future because it is based on bedrock toxicological principles that were developed many decades ago. For all my analyses, I rely only on the post-2012 DOH documents to be consistent with my independent analysis of the more recent 2012 fish tissue PCB levels.

I have identified the following three DOH fish consumption documents most pertinent to my opinion because they provide the most-detailed and relevant information for this case on this particular topic:

1. How Fish Tissue Data Is Used to Develop a Fish Advisory, SRRTTF Workshop, February 9, 2016. McBride, Office of Environmental Public Health Sciences, DOH. [11]
2. *Fish Advisory Evaluation Upper Columbia River Hatchery White Sturgeon 2017.*, April 3, 2018. McBride, Division of Environmental Public Health Office of Environmental Public Health, DOH. [12]
3. *How DOH Develops Fish Advisories.* November 6, 2018. McBride, Office of Environmental Public Health Sciences, DOH. [10]

DOH uses the equation shown in Exhibit 5 and input parameters in Exhibit 6 for all their calculations.

These can be directly use calculated the number of fish meals that are safe to each per month based on an average fish meal weight of 8 ounces or 227 grams. These fish consumption equations and parameters are only intended to protect Spokane fish consumers from developing *noncancer* or systemic organ toxicity and are all based on the RfD as was previously discussed.

Exhibit 5. Noncancer Fish Meal Equation Used to Develop DOH Fish Consumption Advisories [12]

Non-cancer meal equation:

$$\text{Meal per month} = \frac{RfD \times BW \times CF1 \times CF2}{MS \times C}$$

Exhibit 6. DOH Parameters Used to Calculate Fish Consumption Rates [12]

Parameter	Value	Units	Comments	Source
Reference Dose (RfD)	Variable	mg/kg-day	Chemical specific	EPA IRIS or ATSDR MRL
Body Weight (BW)	60 or 70	kg	70 kg adult, 60 kg adult female	EPA Exposure Factors Handbook
Conversion Factor (CF1)	30.44	days/month		
Conversion Factor (CF2)	1000	g/kg		
Meal Size (MS)	227	g	8 oz. meal	DOH
Concentration in fish (C)	Mean contaminant concentration	mg/kg	Specific to species	EPA

These are relatively simple equations that don't requiring making hypothetical assumptions or complex mathematical models as Dr. Keenan has done. The only information necessary to make this calculation is the PCB RfD, which is 0.00002 mg/kg-day. All that needs to be done is to determine how many fish can be eaten so that the daily dose of PCBs in the fish does not exceed 0.00002 mg/kg.

It should also be noted that there are two daily intake toxicity values that can be used to calculate the fish consumption rate. The first, and generally used, source of safe daily intake values is the U.S. EPA Integrated Risk Information System (IRIS), which derives the RfD. The second is ATSDR, which derives Minimal Risk Levels (MRLs). [13] ATSDR takes a very similar approach in developing its MRLs, which are numerically very similar to RfDs. The MRL is defined by ATSDR [13] (which is similar to the U.S. EPA definition of an RfD cited above) as follows:

An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. [13]

To develop its fish advisories, DOH used the chemical-specific toxicity values (RfDs/MRLs) shown in Exhibit 7:

Exhibit 7. DOH RfDs and MRLs Used to Calculate Current Fish Advisories Based on the 2012 Fish Tissue Data [10]

City of Spokane v Monsanto Co.
Expert Rebuttal Report of Richard L. DeGrandchamp, PhD, December 17, 2019

Chemical	Toxicity Value mg/kg-day	Source of Toxicity Value
PCBs	3E-5 2E-5	ATSDR MRL U.S. EPA
Methyl-mercury	1E-4	EPA IRIS
PBDE	1E-4	EPA IRIS

I have verified the toxicity values DOH used are consistent with the most current U.S. EPA IRIS or ATSDR RfDs/MRLs, which are presented in 0. However, DOH used the ATSDR MRL for PCBs that represents intermediate exposures (3×10^{-5}) rather than for chronic exposures (2×10^{-5}). [14]

Exhibit 8. Current Toxicity Values and Critical Effects for Chemicals of Concern in Fish Tissue [15] [16]

Chemical Name	Toxicity Endpoint	Critical Effect or Tumor Type	Toxicity Value Type	Toxicity Value mg/kg-day
PBDE-209	Cancer	Liver neoplastic nodules or carcinoma (combined)	Oral Slope Factor	7x10-4 [5]
PBDE-209	Noncancer	Neurobehavioral effects	RfD	7x10-3 [5]
PBDE-153	Noncancer	Neurobehavioral effects	RfD	2x10-4 [5]
PBDE-99	Noncancer	Neurobehavioral effects	RfD	1x10-4 [5]
PBDE-47	Noncancer	Neurobehavioral effects	RfD	1x10-4 [5]
Aroclor 1254		Ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails; decreased antibody (IgG and IgM) response to sheep erythrocytes	RfD	2x10-5 [5]
Polychlorinated biphenyls (PCBs)	Noncancer	Neurological	ATSDR/MRL Intermediate Exposures	3x10-5 [14]
Polychlorinated biphenyls (PCBs)	Noncancer	Immunological	ATSDR/MRL Chronic Exposures	2x10-5 [14]
Polychlorinated biphenyls (PCBs)	Cancer:B2 (Probable human carcinogen) - based on sufficient evidence of carcinogenicity in animals) (1986 guidelines)	Liver hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas	Oral Slope Factor	2 [5]
Methylmercury (MeHg)	Noncancer	Developmental neuropsychological impairment	RfD	1x10-4 [5]
Methylmercury (MeHg)	Noncancer	Developmental impairment	ATSDR/MRL Chronic Exposures	2x10-5 [14]

Notes:

ATSDR MRL [14]

U.S. EPA IRIS RfD, Slope Factor [5]

Thus, armed with just the RfD (and body weight of the average fish consumer), the number of monthly fish meals can be easily calculated for any species of contaminated fish for any section of the Spokane River.

1.5. DOH-Calculated Fish Consumption Recommendations

DOH has reviewed and analyzed the 2012 fish tissue sampling data and calculated the *mean* or *average* PCB concentration (which I have reviewed and found to be representative). [17] [18] [19] Their calculated mean concentrations and calculated maximum fish consumption rates for each select fish species are presented in Exhibit 9. [10]

Exhibit 9. 2012 DOH Mean Fish Tissue Concentrations and Corresponding Maximum Fish Meal Monthly Rates [10]

2018 Assessment – Cumulative Effects								
Calculated Meal Limits Assuming 50% Reduction in Organics								
Species	PCB sampling data		PBDE sampling data		Mercury sampling data		Combined	Recommendations*
	Mean PCB Aroclor Conc. (ug/kg ww)*	PCB Aroclor Meals/Month*	Mean PBDE Conc. (ug/kg ww)*	PBDE Meals/Month*	Mean Hg Conc. (ug/kg ww)	Hg Meals/Month	Meals/Month*	Recommendation for both PCBs, PBDEs, & Hg*
Spokane Arm								
Largescale sucker (whole)	113.8	1.6	123.3	6.5	60.3	13.3	1.4	1
Brown Trout (fillet)	33.3	5.6	30.4	26.5	85.4	9.4	3.6	4
Rainbow Trout (fillet)	28.8	6.5	8.5	94.7	49.6	16.2	5.2	4
RM 33.7 - Little Falls Pool								
Largescale sucker (whole)	33.0	5.7	20.4	39.5	39.0	20.6	4.8	4
Northern Pike/minnow (fillet)	25.9	7.3	8	100.6	147.0	5.5	3.3	4
RM 56.6-57.1 - Upper Lake Spokane								
Largescale sucker (whole)	126.0	1.5	102.6	7.8	55.3	14.5	1.4	1
Mt whitefish (fillet)	81.6	2.3	159.0	5.1	30.7	26.2	1.7	2
Northern Pike/minnow (fillet)	53	3.5	31.8	25.3	157.0	5.1	2.2	2
Rainbow Trout (fillet)	43	4.4	32.7	24.6	44.1	18.2	3.7	4
RM 64 & 77 - Nine Mile Dam to Up River Dam								
Largescale Sucker (whole)	63.0	3.0	64.1	12.6	25.0	32.2	2.7	2
Mt whitefish (fillet)	125.0	1.5	417.2	1.9	50.0	16.1	0.9	1
Rainbow Trout (fillet)	49.3	3.8	93.4	8.6	36.9	21.8	2.7	2
RM 84.4 & 96 - Upriver Dam to Border (Note: WDFW has closed this area - Catch and Release Only)								
Largescale Sucker (whole)	75.1	2.5	67.0	12.0	46.4	17.3	2.2	2
Northern Pike/minnow (fillet)	21.6	8.7	5.9	136.6	185.0	4.3	3.1	4
Rainbow Trout (fillet)	29.9	6.3	27.7	29.0	36.5	22.0	4.9	4

DOH has had to make some difficult decisions (as all state health departments do) about what type of fish data to use in its Fish Consumption Advisories. DOH has made the reasonable public health decision to use 50% of the detected PCB concentration based on the assumption that 50% of the PCBs will be removed during fish preparation and cooking. While I concur this is a reasonable risk management decision (which is based on a qualitative balance of benefit-risk), the U.S. EPA Fish Advisory [2]

suggests using the full detected concentration to account for those who do not follow the DOH fish advisory recommendations, stating:

Analysis of skinless fillets may also be more appropriate for some target species such as catfish and other scaleless finfish species. In contrast, using whole fish with skin-on as the sample type for assessing PCBs, dioxins/furans, or organochlorine pesticide exposures in populations of Native Americans, Asian Americans, Caribbean-Americans, or other ethnic groups that consume whole fish in a stew or soup is warranted because these contaminants accumulate in fatty tissues of the fish. Cooking the whole fish to make a stew or soup releases the PCBs, dioxins/furans, or organochlorine contaminants into the broth; thus, the whole fish should be analyzed to mirror the way the consumer prepares the fish. Similarly, using skin on fillets with belly-flap included for most other scaled fish to evaluate PCB, dioxin/furan, or organochlorine pesticide exposures in the general fishing population or among recreational fishers is appropriate since this is a standard filleting method (see Sections 7.2.2.6 and 7.2.2.7). This method also allows for the inclusion of the fatty belly flap tissue and skin in which organochlorines, PCBs, and dioxins/furans concentrate and takes into account the fact that some consumers may not neatly trim the more highly contaminated fatty tissue from the edible muscle fillet tissue. [2]

Exhibit 10 shows the number of fish meals corresponding to the fish tissue levels calculated by U.S. EPA and presented in its 2000 fish guidance document. [2] This is important in this case because the DOH-calculated PCB fish consumption advisories Dr. Keenan has critiqued have been used and applied at numerous sites for two decades. Although the U.S. EPA fish consumption rates presented are slightly different from the DOH levels, they were calculated the same way and provide the same number of fish meals. In all respects, they provide the same calculated number of fish meals. The only difference is the manner in which the fish data are presented. While the U.S. EPA numbers present ranges of PCB fish concentrations that correspond to the number of meals, the DOH table presents similar numbers of meals for a specific fish concentration. For example, U.S. EPA calculated that when the fish tissue PCB concentration is between 16 and 23 ppb (note the units in the table are in ppm and have been converted), the maximum number of fish meals is 8. (See Exhibit 10.) A comparison of this result to the DOH table (Exhibit 9) presents a similar result. This is similar to that shown for Northern Pikeminnow at RM 84.4 & 96, as that fish sample had a fish tissue PCB concentration of 21ppb, which falls in the U.S. EPA range of 16–23 ppb; DOH calculated the same number of fish meals that could be eaten. The only reason U.S. EPA could not construct a table identical to the one DOH prepared is because U.S. EPA did not have actual sampling data and, therefore, published a table with bracketed fish tissue PCB concentrations. On the other hand, DOH was able to be very detailed and calculate the specific number of meals based on a specific fish tissue PCB concentration. Both U.S. EPA and DOH used the same equations and the same RfD value.

In addition, the U.S. EPA table presented in 0 provides monthly fish consumption rates for fish tissue PCB based on cancer risk, which are much more restrictive. For example, when the fish tissue PCB concentration exceeds 94 ppb, as indicated in the table, no fish should be eaten. Applying this value to screen the DOH data in Exhibit 9 shows that there would be a total ban on eating three fish. However, 94 ppb represents a risk level corresponding to $1E-5$ (as described in the table notes) and not to the *de minimis* cancer risk level of $1E-6$. If the U.S. EPA table were adjusted to correspond to a *de minimis* bright line of $1E-6$, the fish PCB concentration would be 9.4 ppb; when this risk-based tissue PCB level was compared with the DOH table, there would be a total ban on eating any fish from any site in the Spokane River. Finally, as discussed above, the concentrations presented in the DOH table represent only 50% of the fish PCB concentration that was actually detected.

Exhibit 10. U.S. EPA PCB Fish Consumption Calculations: Presented Fish Risk Assessment 2000 Guidance [2]

Table 4-24. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - PCBs		
Risk Based Consumption Limit ^a	Noncancer Health Endpoints ^b	Cancer Health Endpoints ^c
Fish Meals/Month	Fish Tissue Concentrations (ppm, wet weight)	Fish Tissue Concentrations (ppm, wet weight)
Unrestricted (>16)	0 - 0.0059	0 - 0.0015
16	>0.0059 - 0.012	>0.0015 - 0.0029
12	>0.012 - 0.016	>0.0029 - 0.0039
8	>0.016 - 0.023	>0.0039 - 0.0059
4	>0.023 - 0.047	>0.0059 - 0.012
3	>0.047 - 0.063	>0.012 - 0.016
2	>0.063 - 0.094	>0.016 - 0.023
1	>0.094 - 0.19	>0.023 - 0.047
0.5	>0.19 - 0.38	>0.047 - 0.094
None (<0.5)	>0.38	>0.094

In summary

- ^a The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
- ^b Chronic, systemic effects
- ^c Cancer values represent tissue concentrations at a 1 in 100,000 risk level.
- * Concentration reported in parts per quadrillion (nanogram per kg or 10⁻⁹ g/kg).

Notes:

1. Consumption limits are based on an adult body weight of 70 kg, and RfD of 2x10⁻⁵, and a cancer slope factor (CSF) of 2 (mg/kg-d)⁻¹.
2. NONE = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for PCBs (sum of Aroclors) is 2 x 10⁻² mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

In summary, the DOH fish consumption rate results are supported by U.S. EPA's results that were calculated approximately 20 years ago. DOHs values are as scientifically valid today as they were then. If DOH's fish consumption rates were based on a *de minimis* cancer endpoint, there would be a total ban on eating any fish caught at any point in the Spokane River.

1.6. DOH *De Minimis* Fish Tissue PCB Concentrations


As discussed previously, the U.S. EPA has calculated *de minimis* fish tissue PCB concentrations. While DOH relies solely on the noncancer systemic toxicity endpoint represented by the RfD, it has also calculated the fish PCB tissue level that corresponds to a *de minimis* cancer risk.

These two fish tissue concentrations represent bright lines for evaluating and interpreting the fish tissue data. That is, when the fish tissue concentration is below the *de minimis* concentration defined by the RfD, there should be no concern about potential noncancer systemic toxicity. Likewise, fish tissue samples below the *de minimis* PCB tissue concentrations for cancer will not pose a noncancer health threat nor a significant risk of developing cancer (because the cancer fish tissue concentration is much lower than the noncancer value).

Like U.S. EPA, DOH has calculated the *de minimis* fish tissue PCB consumption rates and the corresponding fish consumption rates. (See Exhibit 11.) However, DOH calculated these values based on the average and upper-bound fish consumption rates of 59.7 and 175 g/day, respectively.

Exhibit 11. DOH Fish Tissue PCB Concentrations: Corresponding to *De Minimis* Cancer Levels for Average and Upper-Bound Fish Consumers [10]

Noncancer endpoint			Cancer endpoint	
$SL_{PCB\ Conc.} = \frac{RfD \times BW}{CR}$			$SL_{PCB\ Conc.} = \frac{ARL \times BW}{CSF \times CR}$	
Analyte	RfD Non-cancer (mg/kg-day)	CSF Cancer (mg/kg-day) ⁻¹	Tissue SL (59.7 g/day) ppb	Tissue SL (175 g/day) ppb
PCB	0.00002	–	23	8
PCB*	0.00003	–	30	10
PCB	–	2	0.59	0.20

 * Based on MRL

As previously discussed, *de minimis* PCB concentrations are based on the safe daily intake of PCBs, which is the RfD for noncancer health effects, or a 1E-6 cancer risk level. DOH only relies on the noncancer toxic endpoint for its fish consumption advisories.

For this reason, it should be stressed that these advisories will not protect Spokane fishermen from elevated cancer risk. DOH shows this separately as another health outcome (Exhibit 11); because of a risk management decision, DOH does not consider cancer risk in the fish consumption advisories. This is because the PCB contaminant levels in fish would have to be significantly reduced from current (2012 PCB levels) to 0.59 and 0.2 ppb for the average and upper-bound fish consumer, respectively, to be protective against cancer at a *de minimis* risk level of one-in-a-million or 1E-6 cancer risk level. All 2012 fish tissue PCB levels far exceed these cancer levels. Indeed, it is clear from the DOH *de minimis* cancer risk levels calculated for PCB-contaminated fish that DOH would have to issue a total fish consumption ban, even when based on fish tissue data that had already been reduced by 50%.

DOH has chosen to calculate the mean fish tissue PCB concentration by assuming 50% of the original PCB concentration will be lost during preparation of the fish meal (removing the skin and cooking). This assumption seems reasonable and may be valid for the typical sport fisherman. Although this assumption will likely be representative of many fish consumers, it does not address the entire population of Spokane River fish consumers, including those who do not understand the fish advisories or because of traditional or ethnic differences in how different groups cook fish. In these cases, assuming a 50% reduced fish consumption concentration would significantly overestimate the number of fish that can be eaten, which could lead to toxic outcomes. That is, for groups who eat the fish whole (as U.S. EPA recommends is assumed), they could be ingesting *twice* the safe amount of PCBs and exceed the RfD by two-fold. Put another way, when interpreting the DOH fish meal recommendations, those who intend to eat the whole fish or who prefer to add the cooked residue oil to their meal should divide the DOH Fish Consumption Advisory by 50%.

My opinion that PCB-contaminated fish may pose health risks to some ethnic groups—even when they do not exceed the maximum allowable number of fish meals—is supported by DOH fish consumption surveys. For example, fish consumers in the Russian community report that an assumption of 50% concentration reduction may not be appropriate for them because they may not remove the skin or cook the fish, and they may eat it whole (minus the head and entrails). Spokane Regional Health District states in its 1998 *Fish Consumption Survey Spokane River, Washington*: [20]

Respondents identified five ways in which they prepare the fish from the Spokane River to eat: cutlets (ground fish-cakes), fried, dried, fish soup, and pickled (herring). The cutlets are prepared by grinding the fish after removal of head and spine; the tiny bones are included in the cutlets. It was reported that a common method to prepare sucker fish to eat was to make cutlets with them. To dry the fish, respondents report, the fish are salted while raw and then dried; they are never

cooked. The whole fish is used when it is dried excluding the intestines and the head. Fish soup is prepared in different ways. Some people use the head others do not. The herring is pickled fish that is stored in a jar and does include bones. [Emphasis added] [20]

It should also be noted that PCBs are virtually indestructible and are not destroyed by cooking (at normal cooking temperatures). Based on professional experience, this fact is contrary to opinions held by some in the general public (expressed to me in many public hearings). Unless the PCB-contaminated fat/oil is decanted off the cooking pan after cooking, the fish advisories will not be health effective in reducing PCB levels. Many fish consumers I have spoken to over the decades at contaminated sites believe the fish oil contains the very nutrients (like omega-3 fat) that they are loath to discard because they (correctly) believe the fish oil is the healthiest part of the fish (fish oil is sold as supplements in capsules and is a very popular nutritional supplement, with a market valued at \$33.04 billion in 2016 [21]) . Some use cooked fish oil to season other parts of their meal or simply pour the oil back over their fish fillet (based on personal interviews). It should be noted that while the DOH Fish Consumption Advice presented in Exhibit 11 does *recommend* eating fish fillets and cooking the fish “so that the fat drips off,” it does not include a statement that consumers should be sure to discard the oil after cooking. It also should also be noted that DOH recommends eating a healthy diet of fish that consists of two fish meals a week. However, a cursory glance at the DOH fish advisory table (Exhibit 9) shows this is not possible due the PCB contaminant level. As the table shows, there is no fish for which it is safe to eat two fish meals per week.

Exhibit 12. DOH Fish Consumption Advice [10]

General Fish Consumption Advice

DOH encourages all Washingtonians to eat at least two fish meals per week as part of a heart healthy diet in accordance with American Heart Association (AHA) recommendations. People may eat fish more than two times weekly, but such frequent consumers should take steps to reduce exposure to contaminants in the fish that they eat by following some general advice.

- Eat a variety of fish that are low in contaminants according to guidance provided on the DOH website at <http://www.doh.wa.gov/fish/>.
- Follow advice provided by DOH and other local health agencies on water bodies to fish.
- Young children and small adults should eat proportionally smaller meal sizes.
- Eat fillets without the skin.
- Consume younger, smaller fish (within legal limits). These fish typically contain lower levels of accumulative contaminants like PCBs and mercury than older, larger fish.
- When cleaning fish, remove the skin, fat, and internal organs before cooking; this will help to reduce the amount of some contaminants.
- Grill, bake, or broil fish so that fat drips off while cooking.

There is evidence that some in the general population do not cook their fish or they eat the entire fish; both of these cases would *not* result in a reduction of the fish tissue concentration by 50%. Although the health goal should be unlimited fish consumption (*ad libitum* fish consumption), this goal is not practical or likely to be achievable for the near future. Therefore, from a health perspective, the most useful and toxicologically meaningful benchmark for the general population who eat Spokane River fish should correspond to how many fish meals are recommended by health professionals and dieticians. There is a consensus among all health professionals that eating fish is vital to maintaining good health, as stated by Washington State DOH:

Fish is a low-fat high quality protein. Fish is filled with omega-3 fatty acids and vitamins such as D and B2 (riboflavin). Fish is rich in calcium and phosphorus and a great source of minerals, such as iron, zinc, iodine, magnesium, and potassium. The American Heart Association recommends eating fish at least two times per week as part of a healthy diet. Fish is packed with protein, vitamins, and nutrients that can lower blood pressure and help reduce the risk of a heart attack or stroke. [2]

DOH also provides a helpful visual aid [2] to show the adjusted body-weight amount (fish tissue weight) that represents a typical fish meal. (See Exhibit 13.) (Fish consumption advisories are typically based on the average adult weight of 60 or 70 kilograms—132 or 150 pounds for women and men, respectively. The calculations I presented in this rebuttal report are based on these two average adult weights.)

Exhibit 13. DOH Weight Adjusted Meal Size [22]

Fish Meal Size		
	A fish meal appropriate to your body size is about the size and thickness of your hand.	
	1 oz. is about the size of an adult thumb. This size would be good for a child that weighs 20 lb.	
Your Weight	Meal Size (uncooked)	
160 lb.	=	8 oz.
140 lb.	=	7 oz.
120 lb.	=	6 oz.
100 lb.	=	5 oz.
80 lb.	=	4 oz.
60 lb.	=	3 oz.
40 lb.	=	2 oz.
20 lb.	=	1 oz.

While the FDA; U.S. EPA; and the National Academy of Sciences, Institute of Medicine (NASIOM) recommend a *minimum* of 8–12 ounces of fish per week (4 meals per month) for the average adult, [2] it is also necessary to consider those who eat more than the minimum number of fish meals. That is, when setting a benchmark or bright line for the number of fish meals that would show PCB levels have been reduced to *de minimis* levels, the number of fish meals needs to be considered, and the number of fish meals must be protective of most of the general population of the general population of Spokane fish consumers, especially those that eat the most fish. That is, while the recommended *minimum* number of fish meals (minimum of 4 per month) there is a sizable portion of the general population that eats Spokane in much greater amounts. That is, the goal is not limited to just protecting the average sport fisherman. The number of meals corresponding to *de minimis* health effects must consider ethnic groups who consume much more Spokane River fish than the average consumer, as well as those groups who rely on subsistence quantities of fish.

1.7. Calculated Fish Consumption Rates for PCB-Contaminated Fish: Full PCB Concentration and 50% Concentration Reduction

To address this credible scenario that some fish consumers will not follow the DOH fish advisories that will reduce the PCB concentration by 50%, I have calculated the maximum number of fish meals to represent Spokane fish consumers who do not cook their fish and/or do not discard the PCB-contaminated fish oil after cooking, as well as those who do. This is of real concern because DOE fish consumption surveys indicate that some groups do not prepare their fish meals in accordance with DOH recommendations. For example, DOE states in its 2013 Fish Consumption Survey: [23]

This telephone survey is part of a broader public outreach and education effort by the Lands Council directed to low-income families, indigenous people, and recent immigrant populations

(Hmong, Vietnamese, Slavic, and Hispanic populations). Selection of these populations was based on previous work conducted by the Spokane Regional Health District, and State Departments of Health and Ecology, and suggests these ethnic populations may be at potential health risks from exposure to contaminants in fish harvested from the Spokane River.

There are a significant number of people catching and/or eating fish from the Spokane River. For those eating fish, few are taking precautionary measures in preparation of the fish.

- *19 percent of respondents fish in the Spokane River.*
- *12 percent catch and eat fish. Over half eat two or more fish in months they are regularly fishing.*
- *Of those who said they eat fish from the Spokane River in a typical year, nearly two-thirds (65%) took no precautions in how they prepared the fish for cooking.*
- *The majority of fishing that includes eating what is caught takes place below Long Lake Dam (80%), where there are no fish advisories regarding consumption.*
- *Some fish consumption not in accordance with the Washington Department of Health fish advisory is occurring between Lake Spokane and the Idaho Border. [23]*

Furthermore, DOH has determined that the average and the upper-bound *daily* fish consumption rates are 59.7 and 175 g/day, respectively. These figures represent a *monthly* fish consumption rate of approximately 8 and 23 meals per month, respectively. Therefore, I use these bright-line consumption rates in my calculations below to interpret and characterize fish consumption to determine whether the monthly calculated fish consumption equals the average and upper-bound fish consumption rates. For example, the *maximum number* of fish meals that can be consumed for any of the PCB-contaminated fish listed for the 2012 fish tissue levels in the DOH Fish Consumption Advisory is 8.7 meals per month for Northern Pikeminnow at the Upriver Dam to the Idaho border. (See Exhibit 14.) At first glance, this could be interpreted to be a considerable number of fish meals, but this needs to be put into context of the average and upper-bound fish consumer; 8.7 fish meals per month is just slightly more than the average fish consumer (8 meals per month) and far below the upper-bound fish consumer (23 meals per month). All other calculated fish consumption rates (0) are below the average fish consumption rate of eight meals per month and well-below the upper-bound rate.

Moreover, the calculated 8.7 meals per month is based on the assumption that the fish tissue PCB concentration will be reduced by 50%. As previously noted, this assumption may not be justified for some groups.

Exhibit 14 presents the 2012 DOH fish data (which I have reviewed and verified) for the full detected PCB mean fish concentrations and the mean concentrations assuming a 50% reduction in edible fish tissue. The corresponding numbers of fish meals are shown for both datasets. This comparison addresses the risks associated with not preparing the fish meal in line with DOH recommendations.

As discussed previously, the maximum number of fish meals that would be safe to eat is solely based on the safe daily consumption rate (RfD). What is noteworthy is that only one out of 15 fish species analyzed from the five sampling locations was low enough that the average fish consumer could eat the *de minimis* number of fish meals. For the upper-bound fish consumer, the results clearly show that the number of fish meals fall far below the *de minimis* number of fish meals they would eat. In short, Spokane River fish are so contaminated with PCBs that the vast majority of fish could not be eaten anywhere close to the average and upper-bound consumption rates when fish consumers do not prepare their fish meals in accordance with the DOH recommendations (i.e., remove the skin, cook the fillet, and discard the oil).

Exhibit 14. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals PCB-Contaminated Fish *With* and *Without* Recommended Fish Meal Preparation

River Section	Fish Species	PCB Results Assuming 50% Reduction in PCB Concentration		PCB Results No Reduction in PCB Concentration	
		50% Mean PCB Aroclor Conc. (ug/kg ww)	PCB Aroclor Meals/Month	Total Mean PCB Aroclor Conc. (ug/kg ww)	PCB Aroclor Meals/Month
Spokane Arm	Largescale sucker (whole)	113.8	1.6	227.6	0.8
	Brown Trout (fillet)	33.3	5.6	66.6	2.8
	Rainbow Trout (fillet)	28.8	6.5	57.6	3.3
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	5.7	66	2.8
	Northern Pikeminnow (fillet)	25.9	7.2	51.8	3.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	1.5	252	0.7
	Mt whitefish (fillet)	81.6	2.3	163.2	1.1
	Northern Pikeminnow (fillet)	53	3.5	106	1.8
	Rainbow Trout (fillet)	43	4.4	86	2.2
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	3.0	126	1.5
	Mt whitefish (fillet)	125	1.5	250	0.7
	Rainbow Trout (fillet)	49.3	3.8	98.6	1.9
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	2.5	150.2	1.2
	Northern Pikeminnow (fillet)	21.6	8.7	43.2	4.3
	Rainbow Trout (fillet)	29.9	6.3	59.8	3.1

Notes:

DOH 2012 Data [17]

Assuming BW=70 kg; U.S. EPA RfD=0.00002

Orange Highlight = Average *de minimis* fish consumption rate of 8 meals/month

Additionally, as I discussed in Volume 3 of my expert report, PCB health risks are based on, and are proportional to, the PCB concentration. For example, a reduction in the PCB loading to the river producing a 10% reduction in fish tissue PCB concentrations will reduce the calculated health risk by 10%. This relationship also holds for the fish consumption advisory shown in Exhibit 14. For example, in the first row, the number of largescale sucker meals for the full PCB concentration is 0.8, while the number of meals is doubled to 1.6 meals for the same fish assuming the PCB concentration is 50%.

1.8. Calculated Fish Consumption Rates for PBDE-Contaminated Fish

Dr. Keenan critiqued my report because he stated that I ignored other contaminants.

In addition to PCBs, fish have been shown to be contaminated with polybrominated diphenyl ethers (PBDEs), which are flame retardants used in a variety of consumer and industrial products [24] and are complex mixtures of 209 individual PBDE congeners. The 2012 fish sampling data include individual sampling results for 13 PBDE congeners (i.e., PBDE-049, -066, -071, -138, -153, -154, -183, -184, -191, -209, -047, -100). U.S. EPA has developed RfDs for four PBDE congeners.

DOH has calculated the mean PBDE concentrations for fish tissue, as shown in Exhibit 15. (I have reviewed these and find they are representative of PBDE fish contamination levels). Based on the mean concentration, I calculated the number of fish meals per month fish consumers could eat without experiencing toxic effects.

What is noteworthy about these results in comparison with Exhibit 14 is that, because PBDE is much less toxic than PCBs, many more fish meals can be eaten when comparing PBDE to PCBs. (The U.S. EPA RfDs for PCBs and PBDE are 0.00002 and 0.0001, respectively, making PCBs five times more toxic than PBDEs). It should be noted that the PBDE concentrations, like the PCB concentrations above, have been reduced by 50%, so this comparison is an “apple-to-apple” comparison to above PCB numbers presented in column 2 of Exhibit 14.

As shown in Exhibit 15, the average Spokane fish consumers can eat the *de minimis* number of fish meals for some species at *all* five fish sampling locations. For specific fish species, the highlighted (orange- plus green-shaded) boxes show that 11 out of 15 (73%) of the fish sampled at the five locations can be eaten at *de minimis* average fish consumption rates (8 meals/month). Moreover, the table also shows that the PBDE levels are sufficiently low that, even for upper-bound fish consumers (23 meals/month), 8 out of

the 15 fish (more than half or 53%) samples are below toxic levels and they can eat the number of *de minimis* number of fish meals.

These results are in stark contrast to the PCB results shown in Exhibit 14 in which there was only one species at one location where tissue PCB concentrations would permit average fish consumers to eat *de minimis* amounts of fish tissue (assuming 50% PCB concentration reductions, as were assumed here for PBDE).

Exhibit 15. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals—PBDE-Contaminated Fish

River Section	Fish Species	PBDE Results Assuming 50% Reduction in PBDE Concentration	
		Mean PBDE Conc. (ug/kg ww)	PBDE Meals/Month
Spokane Arm	Largescale sucker (whole)	123.3	6.5
	Brown Trout (fillet)	30.4	26.4
	Rainbow Trout (fillet)	8.5	94.5
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	20.4	39.4
	Northern Pikeminnow (fillet)	8	100.4
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	102.6	7.8
	Mt whitefish (fillet)	159	5.1
	Northern Pikeminnow (fillet)	31.8	25.3
	Rainbow Trout (fillet)	32.7	24.6
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	64.1	12.5
	Mt whitefish (fillet)	417.2	1.9
	Rainbow Trout (fillet)	93.4	8.6
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	67	12.0
	Northern Pikeminnow (fillet)	5.9	136.2
	Rainbow Trout (fillet)	27.7	29.0

Notes: DOH 2012 Data McBride [10]

Assuming BW=60 kg; U.S. EPA RfD=0.0001

Green Highlights = Upper-bound *de minimis* fish consumption rate 23 meals/month

Orange Highlights = Average *de minimis* fish consumption rate 8 meals/month

1.9. Calculated Fish Consumption Rates for Mercury-Contaminated Fish

Like PBDEs discussed above, Spokane fish are also contaminated with Hg. However, unlike PCBs and PBDE, Hg is not a manufactured commercial synthetic contaminant. It has a Statewide ubiquitous distribution and is correctly characterized as an environmental background chemical. It is both a naturally occurring background element present in rock and soils and is also an anthropogenic background chemical (released from man's activity, often from fuel combustion). It is largely an airborne contaminant (that crosses state boundaries) that contaminates water bodies as a result of deposition and subsequent surface runoff into water bodies. Spokane River fish have been found to contain Hg.

Exhibit 16 shows the DOH mean Hg concentration for the same fish that were analyzed for PCBs and PBDEs (Exhibit 14 and Exhibit 15). The major difference between PCBs and PBDE, and Hg, is that PCBs and PBDEs are primarily stored in fish fat tissue, while Hg is not. Hg is largely bound to proteins in fish muscle tissue rather than to fat, so cooking has no effect on reducing the Hg concentration. The major chemical form of Hg in fish tissue is methyl-mercury, which is the bioaccumulative form of Hg (elemental Hg is not typically bioaccumulated). Accordingly, the Hg concentrations presented in Exhibit 16 represent the full laboratory Hg concentrations.

I have conducted the same analyses on the Hg fish tissue results as I described above for PCBs and PBDEs. That is, I assumed Hg is the only contaminant present in fish tissue in order to isolate Hg and determine the number of fish meals that can be eaten solely attributable to this one contaminant.

The results for Hg are strikingly similar to those I discussed for PBDE-contaminated fish above. Again, some fish species can be eaten at *de minimis* fish consumption rates for all sections of the river. Twelve fish samples out of 15 (80%) had Hg levels low enough to permit the average fish consumers to consume the *de minimis* number of fish meals (8 meals/month). For the upper-bound fish consumer (23 meals/month), two fish samples (2/15) had Hg levels low enough to allow *de minimis* fish consumption. However, it should be noted that, while the number of fish samples for upper-bound *de minimis* fish consumption were less than I showed and discussed above for PBDE (8/15), the Hg fish concentrations for many samples were well above the average *de minimis* levels. For example, three fish samples had Hg levels that would allow more than 20 meals per month, and the rest were also well above the average *de minimis* average rate of eight meals per month.

Exhibit 16. Noncancer Health Effects, 2012 Data: Maximum Allowable Fish Meals—Hg-Contaminated Fish

River Section	Fish Species	Mean Hg Conc. (ug/kg ww)	Hg Meals/Month
Spokane Arm	Largescale sucker (whole)	60.3	13.3
	Brown Trout (fillet)	85.4	9.4
	Rainbow Trout (fillet)	49.6	16.2
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	39.0	20.6
	Northern Pikeminnow (fillet)	147.0	5.5
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	55.3	14.5
	Mt whitefish (fillet)	30.7	26.2
	Northern Pikeminnow (fillet)	157.0	5.1
	Rainbow Trout (fillet)	44.1	18.2
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	25.0	32.1
	Mt whitefish (fillet)	50.0	16.1
	Rainbow Trout (fillet)	36.9	21.8
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	46.4	17.3
	Northern Pikeminnow (fillet)	185.0	4.3
	Rainbow Trout (fillet)	36.5	22.0

Notes: DOH 2012 Data McBride [10]

Assuming BW=60 kg; U.S. EPA RfD=0.0001

Green Highlights = Upper-bound *de minimis* fish consumption rate 23 meals/monthOrange Highlights = Average *de minimis* fish consumption rate 8 meals/month**1.10. Dr. Keenan Stated I Ignored Lead as a Contaminant**

The last contaminant Dr. Keenan stated I ignored was lead (Pb). I did not ignore it. I conducted a toxicological analysis of Pb, but did not include it in my report because it is not possible to quantitatively evaluate it like I did for PCBs, PBDE, and Hg for the simple reason that Pb does not have an RfD. Neither U.S. EPA nor ATSDR has developed an RfD for Pb. Therefore, it cannot be evaluated together with the other three contaminants.

As I have discussed, both U.S. EPA and DOH fish risk assessment guidance presents the same equation for evaluating and quantifying the risks and safe fish consumption rates for multiple contaminants. (See Exhibit 17). [2] [12] In fact, this is the exact equation that DOH used to evaluate Spokane River fish (for the 2012 DOH data), and it was used just as presented to support the current Fish Consumption Advisory; it is obvious that Pb was not included in DOH's quantitative analysis.

Exhibit 17. DOH Equation for Calculating the Risks and Fish Consumption Rates for Multiple Contaminants [12]

$$\text{Meals per month} = \left(\frac{BW \cdot CF}{MS} \right) \cdot \left(1 / \left(\left(\frac{C_{\text{mercury}}}{RfD_{\text{mercury}}} \right) + \left(\frac{C_{PBDE}}{RfD_{PBDE}} \right) + \left(\frac{C_{PCB}}{MRL_{PCB}} \right) \right) \right)$$

It should be noted that the first consumption advisory was intended to warn the public about the number of meals that were safe to eat in terms of both PCBs and Pb. It focused on the same fish species that were sampled in the 1999 U.S. Geological Survey (USGS)/Washington State DOH report—namely, rainbow trout, mountain whitefish, and largescale suckers. The warning for Pb exposures only seems to have been applied as a precautionary note for consuming the “nonedible” parts of the fish and was thus issued for eating the whole fish. However, this was based on the specific wording of the one-page Fact Sheet and the supporting 1999 USGS and other fish data, since I was unable to locate the entire 2001 Washington State DOH Health Advisory. [25]

While the fish advisory applied to both whole fish and fillets for PCB contamination, the Health Advisory (which appears to err on the side of caution) also noted that there was a potential health threat from Pb-contaminated fish, but only applied to consuming whole fish” for Pb. It did not apply to fish fillets, as stated in the following section of the Health Advisory:

What are the harmful effects of PCBs and lead? Who should be concerned? Pregnant women and women considering pregnancy should carefully follow the meal limits given in table 1.

*The fetus is particularly susceptible to the harmful effects of lead and PCBs when the mother eats contaminated fish. Such effects can include learning problems that appear during childhood years. Negative effects on a child's behavior and ability to learn can also occur in children exposed to lead from birth through six years of age. **Because lead was found at higher levels in whole fish samples, it is especially important for children under age six to eat only fillets according to the meal limits in table 1.** [original emphasis] [25]*

As the Health Advisory emphasis indicates, Pb was only a concern when consuming whole fish. The reason for this distinction is that, unlike PCBs, which are bioaccumulated in all fat-containing tissues and organs in fish, Pb is not. After Pb is absorbed by fish, it is sequestered and stored in nonedible fish parts like the gills, bone, kidney, spleen, and intestines, but the bone is the most likely. It is largely sequestered into bone, where it substitutes for calcium. This type of absorption and sequestration into bone is similar to how the human body stores Pb. Consequently, and most importantly, Pb does not bioaccumulate in fish muscle tissue, so the only concern with Pb in typical fish advisories pertains to eating the whole fish—including bone and gills. This opinion is supported by the detailed analysis later addressed and carefully analyzed in the 2007 ATSDR/Washington State DOH Health Consultation for Spokane River fish in which a determination was made to eliminate Pb as a chemical of concern, as it was shown that consuming fish fillets would not pose a health threat (i.e., muscle tissue fillets contain 10 times less Pb than the nonedible whole-fish body parts). [26]

With regards to lead, Washington State DOH issued advice against eating whole fish because USGS studies showed fish fillets from Spokane River fish did not bioaccumulate Pb—even those fish caught in river areas known to be highly enriched with Pb-laden mining waste. The 1989 USGS study (Maret and Skinner 1989; published 2 years before the 2001 Health Advisory) showed fish analyzed from Spokane River sections known to be downstream of mining production sites had insignificant bioaccumulation of any heavy metal, including Pb, in fillet muscle tissue. In fact, the USGS showed there was a “poor correlation” between the paired highly contaminated heavy metal sediments in mining areas (save for Cd) and the corresponding fish tissue levels in those areas. USGS stated:

Correlations between most trace-element concentrations in bed sediment and tissue (livers and fillets) were poor; however, there was a significant correlation between Cd in bed sediment and liver tissue. Trace-element concentrations in bed sediment did not appear to be good predictors of concentrations in tissue... [25]

In addition to discussing the very important concept that heavy metals did not bioaccumulate in fish, work by USGS (1989) showed that the fish tissue levels—even in highly enriched sediments—were below the U.S. EPA sediment screening values (SV) that were developed for bed sediments and edible fish tissue. (SVs were defined as “associated adverse effects to aquatic life or human health are possible, but expected infrequently”; USEPA tissue SVs were protective of human health at a “ 1×10^{-5} risk factor” based on an average-sized adult (70 kilograms) and a consumption rate of 6.5 grams of fish per day (or approximately 45 grams of fish per week). USGS stated:

Even though many of the sites exhibited trace-element enrichment, no trace-element concentrations in sportfish fillets exceeded USEPA SVs. This is noteworthy, because Pb and Hg can bioaccumulate in aquatic biota and are pollutants of concern around mining sites in the study area. It is apparent from this study that trace elements in bed sediment are not readily bioavailable for uptake by fish, especially the trace elements As, Cd, Pb, Hg, and Se, which are known to bioaccumulate in aquatic food chains. [25]

Finally, even in areas in which the riverbed Pb sediments were greatly enriched to levels higher than 100 ppm, no Pb bioaccumulation was seen in fish livers or fillets:

Although concentrations of Pb were high ($>100 \mu\text{g/g}$) in bed sediment at some NROK [Northern Rockies Intermontane Basins] sites, Pb did not tend to accumulate in fish livers or fillets. This finding is particularly important because Pb has been identified as a pollutant of concern to humans and wildlife as a result of mining activities in this study area. [25]

It is well-known that when fish (as well as mammals) ingest contaminated sediments or prey containing Pb, it does not build up in muscle tissue. Rather, most of the Pb body burden is found in bone, gills, liver, and kidney:

Lead can accumulate in bones, scales and skin (by sticking on to the skin surface). Lead can also be introduced from mucus and organs. [26]

Because Pb is sequestered in fish tissues and organs that may only be eaten rarely (if ever), the agencies state that whole-fish samples are “not appropriate” for human health risk assessment:

However, because whole largescale sucker rather than the edible portion (fillets) were analyzed for suckers, the values reported are not appropriate for human health risk assessment.

Furthermore, they assumed that children would not only eat whole fish, but that they would also consistently eat *only* the fish species with the highest whole-body Pb level—namely, largescale suckers. By their own admission, they did not think this a reasonable assumption: “However, it is highly unlikely that a child would consume only largescale suckers.” [26]

Lacking an RfD, Pb-related risks cannot be evaluated in the same manner as other contaminants. Therefore, I chose to evaluate Pb from a toxicological standpoint. I have concluded that Pb-contaminated fish would not pose a health hazard even when the whole fish are eaten. This is because Pb is primarily bound to bones in fish and the chemical bond is so strong that even if a fish consumer ate the entire fish including bone, Pb would not be appreciable released from bone in the human gastrointestinal tract which is necessary for absorption into the body. That is, for Pb to be absorbed from the human gastrointestinal tract it must first be *desorbed* from the fish bone and because Pb is not desorbed from bone tissue (due to

the very strong chemical bond) it will not be significantly absorbed into the systemic blood circulation by the fish consumer.

If, for example, even when whole fish (bones and all) are used to make a stew or soup, Pb would not be significantly released into the water and most would still be bound to bone tissue. Furthermore, assuming a fish eater actually ate the bones it would not be in a *bioavailable* chemical form that could be absorbed from the microvilli lining the small intestine where most absorption occurs.

Simply put, Pb will not be bioavailable due to the tenacious stable chemical forces holding it in place in bone. Pb actually becomes part of the bone matrix. This is not just true in fish but when humans are exposed to Pb is stored for decades in bone tissue (which can be viewed as a protective physiological mechanism because only *free* unbound Pb can cross the blood brain barrier to cause brain damage and as long as it stored in bone it is not free).

When Pb is ingested by fish, it is sequestered into skeletal bone by forming a nearly unbreakable bond with the phosphate mineral apatite—which is the chemical structure of bones—to form pyromorphite; this stable crystalline mineral cannot be absorbed by the human digestive system (Freeman 2012). [27] For example, Miretzky et al. (2008) states that intentional or unintentional ingestion of pyromorphite does not pose a health threat because it cannot be made soluble in the physiological conditions of the gastrointestinal tract: [28]

Accidental pyromorphite ingestion does not yield bioavailable lead, because pyromorphite is insoluble in the intestinal tract.

In fact, bone acts like a sponge to absorb Pb, and the resulting pyromorphite is so incredibly stable that it has been shown to be very effective biomaterial tool for remediating Pb-contaminated water at polluted sites: [27]

Adsorption onto biomaterials is one of the most promising processes for heavy metal remediation of contaminated water...The percent lead removed from the contaminated aqueous solution by each fish bone, carbonate and phosphate salt was calculated. Lead removal by the fish bone was greater than 99% for each type of fish bone used. The results further suggest that the fish bones removed slightly more lead than sodium carbonate and sodium phosphate. These results suggest that unmodified fish bone is a highly effective biomaterial for removing lead from contaminated water.

Ground fish bones are even effective in sequestering Pb from contaminated soils: [27]

Now researchers are using fish bones and other phosphate-rich amendments to remediate lead in urban soils. "We have seen reduction in bioaccessibility in some lab samples up to fifty percent

within just a few weeks of treatment,” says Steve Calanog of the U.S. Environmental Protection Agency (EPA), who is overseeing an agency project using fish bones to clean up soils in the South Prescott neighborhood of Oakland, California.

Pb stored in skeletal bone is essentially considered a protective toxicological mechanism in both fish and humans because it immobilizes Pb in the body in the solid bone matrix and prevents Pb-induced toxicity (Pb remains bound in bone for many decades). This is because only free or unbound Pb can reach the brain from the systemic blood circulation. This is a well-known fundamental principal in toxicology, which was even stated in the Health Consultation, but only in reference to human exposures:

Because of chemical similarities to calcium, lead can be stored in bone for many years. Even after exposure to environmental lead has been reduced, lead stored in bone can be released back into the blood where it can have harmful effects. Normally this release occurs relatively slowly.
[26]

In summary, the degree to which absorption of Pb into the human body after eating fish tissue contaminated with Pb depends on a variety of factors but the *sine qua non* is Pb bioavailability, as discussed previously. That is, in order for Pb to produce neurotoxic effects in a child, it must first be absorbed into the child's body from the gastrointestinal tract after a fish meal. Once the Pb-contaminated fish tissue reaches the stomach and small intestine, Pb must first be made *bioaccessible*; unless it is solubilized from fish tissue, it cannot be absorbed in the duodenum (the first part of the small intestine that is attached to the stomach). Bioaccessibility describes the process whereby Pb is first desorbed (the opposite of absorbed) from solid fish tissue matrixes like fish bone and other tissues in which it is made water-soluble and can be dissolved in the watery intestinal contents. Desorption from the solid state matrix is an absolute requirement for Pb because it must be soluble in the aqueous environment of the gastrointestinal tract (absorptive tissue lining the small intestine) in order for it to be transported through the cells lining the small intestine (gastrointestinal epithelium). Only the water-soluble fraction of Pb can pass through the cells lining the intestine, reach the intestinal blood capillaries, and enter the systemic blood circulation (via the hepatic portal vein). The portion that remains nonsoluble and bound to the solid fish tissue matrix cannot be absorbed, and that fraction will simply be eliminated in the feces. The percent bioavailability is one of the most important assumptions used in the U.S. EPA Pb models for calculating the BBL. The Health Consultation recommendation for eating whole fish contaminated with Pb is based on the assumption that 30% of the Pb in whole fish is bioavailable. Since Pb bound to fish bone represents the largest fraction in all fish organ systems and the Pb–bone fraction is not bioavailable, the bioavailability assumption of 30% Pb for children overestimates the BBL and risk to children.

1.11. Comparing the Maximum Allowable Fish Meal PCB Levels with Multiple Contaminants

In the previous sections, I evaluated the three fish contaminants separately, assuming only one contaminant was present in fish. Comparing those results shows that it is obvious that PCB is the greatest threat to Spokane fish consumers, and it is the most important contaminant that needs to be targeted by the City for remediation.

In this section I present the results in a somewhat different format. While the previous section allowed a side-by-side comparison of the three contaminants, it did not permit an evaluation of the health threat when just PCBs were removed from fish tissue. Therefore, it would be useful to know if fish consumers could eat more fish if Spokane's efforts succeeded in removing PCBs. For this analysis, I compared the maximum allowable fish meals based on all three contaminants (PCBs + PBDEs + Hg) being present (using 2012 data) to the scenario where Spokane was successful in removing PCBs, leaving only Hg and PBDEs in the fish tissues. This is the generally accepted toxicological practice of analyzing the magnitude of a single contaminant when investigating chemicals that all target the same body organ. In this analysis, the summed risks can be added since all three contaminants produce similar toxic effects in the central nervous system, causing neurological damage (particularly during development in young children and adolescents).

Ultimately, this analysis addresses the question, "Will remediating PCBs have a significant impact on fish consumption, even though fish will still be contaminated with other chemicals?" (i.e., is it worth it?). The answer is yes.

The calculated number of maximum fish meals will be significantly increased if PCBs are reduced even if PBDE and Hg are assumed to remain unchanged from 2012 levels. The table below in Exhibit 18 shows: 1) the number of fish meals that can be safely consumed for fish tissues contaminated with all three chemicals (PCBs, PBDE, and Hg); and 2) the maximum number of fish meals assuming PCBs are no longer in the fish. The first column shows the combined effect on fish meals resulting from the combined effect of just PBDE, and Hg this is juxtaposed with column 3 that shows that number meals is significantly decreased with all three contaminants (i.e., PCB + PBDE + Hg). The last column shows the increased number of fish meals in multiples when PCB is assumed to be absent from fish tissues. For example, the first row shows that when all contaminants are present only 1.4 fish meals can be eaten but

when PCB are removed, the number of meals is significantly increase to 4.4 meals, which is 3.1 times as many meals

Exhibit 18. Noncancer Health Effects, 2012 Data: Comparing the Maximum Allowable Fish Meals, With and Without PCB Contamination

River Section	Fish Species	Maximum Allowable Fish Meals- <i>PCBs Eliminated</i>	Maximum Allowable Fish Meals With <i>All</i> Contaminants	Differences In Multiples (x)
		ONLY=PBDE + Hg	ALL=PCBs + PBDE + Hg	
Spokane Arm	Largescale sucker (whole)	4.4	1.4	3.1
	Brown Trout (fillet)	6.9	3.5	2.0
	Rainbow Trout (fillet)	13.8	5.2	2.7
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	13.5	4.7	2.9
	Northern Pikeminnow (fillet)	5.2	3.3	1.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	5.1	1.4	3.7
	Mt whitefish (fillet)	4.2	1.7	2.4
	Northern Pikeminnow (fillet)	4.3	2.2	1.9
	Rainbow Trout (fillet)	10.5	3.7	2.9
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	9.0	2.7	3.4
	Mt whitefish (fillet)	1.7	0.9	1.9
	Rainbow Trout (fillet)	6.2	2.7	2.3
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	7.1	2.2	3.2
	Northern Pikeminnow (fillet)	4.2	3.1	1.4
	Rainbow Trout (fillet)	12.5	4.9	2.6
Average Difference				2.5

Notes: DOH 2012 Data McBride [10]

Assuming BW=60 kg; U.S. EPA RfD=0.0001 for Hg and PBDE; PCB RfD 0.00002

Orange Highlights = Average *de minimis* fish consumption rate 8 meals/month

This increase in the number of meals when PCB is reduced to zero has real-like consequences. That is, with PCB gone, fish consumers can enjoy the health-benefits of eating the *de minimis* recommended number of 1 fish meal per *week*. In fact, after PCBs are eliminated, the recommended number of fish can be eaten for all fish samples.

1.12. Rebuttal Response to Dr. Keenan's Critique of the Fish Consumption Rate

Dr. Keenan makes the following statements on page 6-3:

Dr. DeGrandchamp provides a discussion of risks associated with the ingestion of fish at a rate of 42 g/day (on average) and 90 g/day for higher-end consumers. As I discussed in Section 5.2, the 42 g/day fish ingestion rate presented by WDOH (2007), which was cited as based on studies conducted in the late 1990s that were not specifically designed to estimate fish consumption rates, is likely in error. A similar consumption rate was reported in ATSDR (2005). Even so, WDOH uses the 42 g/day value only in its screening assessment. Fish advisories are set assuming an 8-oz meal size, which equates to 32 g/day for one fish meal per week. The error associated with the 42 g/day consumption rate also puts into question the derivation and use of the higher end consumption rate of 90 g/day.

Dr. Keenan is incorrect for several reasons. First, DOH does not use 42 g/day in its screening assessment. As I discussed previously, it uses 59.7 and 175 as fish ingestion rates to represent the average and upper-bound screening levels, as shown in Exhibit 19. (I have referred to these screening levels as *de minimis* fish tissue concentrations).

Exhibit 19. DOH Uses 59.7 and 175 g/day to Calculate Screening Levels

Fish Tissue Screening Levels (SL)				
Noncancer endpoint			Cancer endpoint	
$SL_{PCB\ Conc.} = \frac{RfD \times BW}{CR}$			$SL_{PCB\ Conc.} = \frac{ARL \times BW}{CSF \times CR}$	
Analyte	RfD Noncancer (mg/kg-day)	CSL Cancer (mg/kg-day) ⁻¹	Tissue SL (59.7 gm/day) ppb	Tissue SL (175 gm/day) ppb
PCBs	0.00002		23	8
PCBs		2	0.59	0.2
PBDEs	0.0001		100	34
Mercury	0.0001		100	34

Second, as I discussed previously, health groups and governmental agencies recommend that a healthy diet consist of 8–12 ounces of fish per week [29], which equals 32–48 g/day; this is considered the minimum daily fish ingestion rate. Exhibit 20 shows the recent recommendation by U.S. EPA–FDA for the number of fish meals pregnant women or women of childbearing age.

Exhibit 20. U.S. EPA–FDA Recommends 8–12 Ounces of Seafood per Week
[3]

Serving size is also consistent with the recommendation of 8-12 ounces of a variety of seafood per week from choices lower in methyl mercury found in the Dietary Guidelines for Americans 2015 and USDA's. This is equivalent to 2-3 four-ounce servings per week.

Weekly servings = 1, 2, or 3

Indeed, U.S. EPA–FDA also used a fish ingestion rate of 48 g/day (three 4-ounce servings) to calculate a screening level for eating Hg-contaminated fish. The agencies characterized this fish ingestion rate as being the healthiest, labeling it among “Best Choices” to encourage women to eat more fish. (See Exhibit 21.)

Exhibit 21. U.S. EPA–FDA Hg Fish Contamination Screening Levels Based on a Fish Ingestion Rate of 48 g/day Is among “Best Choices” [3]

Weekly fish servings	Screening value (µg/g)	Chart category
1	≤ 0.46	Good Choices
2	≤ 0.23	
3	≤ 0.15	Best Choices

Contrary to Dr. Keenan’s opinion that a fish ingestion rate of 42 g/day may not be appropriate, it should be noted that when DOH set the assumed fish ingestion rate to 42 g/day, it essentially set a fish ingestion below even the minimum fish ingestion rate governmental health agencies recommend. [29]

Dr. Keenan also states on page 6-6:

Dr. DeGrandchamp also did not closely review WDOH’s quoted risk results. These risk results were based on a consumption rate of 42 g/day, which, as stated earlier, is an error. The risk calculations should have been based on an 8-oz meal size, which equates to 32 g/day (at one fish meal per week). Use of this elevated fish consumption rate overestimates the potential risks by a factor of 1.3 (42/32).

The document Dr. Keenan is referring is the *1997 Consumption Patterns of Anglers Who Frequently Fish Lake Roosevelt*, September 1997, DOH. [20] As I stated in my deposition, I reviewed this document to determine the source of the fish ingestion rate of 42 g/day. However, but since no raw data were presented, I evaluated the summary data in which DOH did present numerical estimates of the fish consumption rates. [20]

The above data within the report supports my opinion that a consumption rate of 42 grams per day is a reasonable fish consumption rate that will protect a large number of people eating PCB-contaminated fish. As I repeatedly stated in my deposition, the overarching goal of all health assessments intended to protect public health is to prevent the majority of the public—not just the average fish consumer—from eating an excessive amount of PCB-contaminated fish. As noted above, the fish consumption survey stated that the average fish consumption was 42 fish meals per year, which equates to an average (50th

percentile) daily fish consumption of 26 grams. However, the 90th percentile of those surveyed consumed 103.2 meals per year, or two meals per week, which is equivalent to 64 g/day. Thus, the fish ingestion rate of 42 g/day falls in the middle of these two consumption rates (i.e., 45 g/day), approximately corresponding to the 75th percentile. As I testified in my deposition, a 42 g/day ingestion rate was a reasonable assumption, as it protects about 75% of the population. Although it does not protect the entire population (with the target being 90%–95%), it is more protective than the 26 g/day average consumption rate, which only protects half the population. Therefore, while I did not cite this particular document in my expert report, the findings are not inconsistent with my opinion.

In addition, DOH stated that the primary target was license holders and fishing club members, which would have ignored those fishing without a license and those not belonging to a club:

A mail survey questionnaire sampled two fish-consuming populations based on a random sample of Spokane County fishing license holders (2000 sample population) and individuals from a particular Spokane area fishing club (180 sample population from The Walleye Club). [20]

Part of that survey also included fishing consumption rates for ethnic groups like the Russian community. DOH concluded the rate for that group was 65 g/day: [20]

Key Russian Community Findings:

- *Harvest locations: Upriver Dam, the old Walk in the Wild Zoo, River Front Park, downtown Spokane area, T.J Meenach Bridge, Nine Mile Bridge, and Long Lake.*
- *Fish harvested: rainbow trout, German (brown) trout, suckers, catfish, crayfish, pike minnow, smallmouth bass, and perch.*
- *Fish consumption: about 4 pounds per month (about 65 g/day or 2.3 ounces of fish per day).*

1.13. Calculated Noncancer Hazard Quotient and Cancer Risk

Assuming higher ingestion rates – which are reflected by the above-discussed documents -- would significantly increase the risk under Keenan’s analysis. In my above response to Dr. Keenan’s critique that a fish ingestion rate of 42 g/day is not appropriate, I state that it is a reasonable assumption because it falls below even the *minimum* fish ingestion rates that are recommended by governmental health agencies. [29] In this section, I calculate the PCB noncancer hazard index and cancer risk (using the 2012 DOH fish tissue dataset) based on the fish ingestion rates that are the subject of this issue: 42 g/day. I

have also calculated the same hazards and risks assuming 64 g/day, since that was the 90th percentile for the fish ingestion rate.

I should also stress that the fish ingestion rate of 42 g/day is not germane to my opinion because using that assumption—which corresponds to about the 75th percentile (the 50th and 90th percentiles were 26 and 64 g/day, respectively) does not protect the entire population. The generally accepted practice in toxicology and risk assessment is to protect the entire population, which corresponds to the 95th–99th percentile; that would be greater than even the 90th percentile level of 64 g/day.

1.13.1. Equations for Calculating Daily PCB Dose from Eating PCB-Contaminated Fish

Noncarcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Dose}_{\text{noncancer}} (\text{mg/kg-day}) = [(C * CF_1 * IR * CF_2 * EF * ED) / (BW * AT)]_{\text{noncancer}}$$

Carcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Dose}_{\text{cancer}} (\text{mg/kg-day}) = [(C * CF_1 * IR * CF_2 * EF * ED) / (BW * AT)]_{\text{cancer}}$$

Noncancer Hazard Quotient

$$HQ = \text{Dose}_{\text{noncancer}} / \text{RfD}$$

Carcinogenic: Equation for Fish Tissue Exposure Dose

$$\text{Cancer Risk} = \text{Dose}_{\text{cancer}} * \text{CSF}$$

Exposure parameters and values used to calculate PCB dose are shown in Exhibit 22.

Exhibit 22. Exposure Assumptions for Calculating the HQ and Cancer Risk

Parameter	Value	Unit	Comments
Concentration (C)	Variable	ug/kg	Mean Fish Tissue Concentration
Conversion Factor (CF ₁)	0.001	mg/ug	Converts contaminant concentration from micrograms (ug) to milligrams (mg)
Ingestion Rate (IR)	42 and 64 g/day	g/kg/day	Average recreational anglers (42 g/day)
Conversion Factor ₂ (CF ₁)	0.001	mg/ug	Converts contaminant concentration from micrograms (ug) to milligrams (mg)

Conversion Factor ₂ (CF ₂)	0.001	kg/g	Converts mass of fish from grams (g) to kilograms (kg)
Exposure Frequency (EF)	365	days/year	Assumes daily exposure consistent with units of ingestion rate given in g/day
Exposure Duration (ED)	30 (adult)	years	Number of years eating fish
	5 (child)		
Averaging Time <i>noncancer</i> (AT)	10950	days	30 years
Averaging Time <i>cancer</i> (AT)	25550	days	70 years
Oral Reference Dose (RfD)	2E-5	mg/kg-day	Source: USEPA, IRIS (2019)
Cancer Slope Factor (CSF)	2	mg/kg-day ⁻¹	Source: USEPA, IRIS (2019)

Exhibit 23 presents the hazard quotients for PCB-contaminated fish using the 2012 DOH data and assuming a fish ingestion rate of 42 g/day for both the 50% PCB concentration and the full PCB concentration. As this table shows, more than 11 of the fish samples (11/15; 73%) exceeded the safe daily intake (based on the RfD), which is HQ = 1.0. All HQ results exceeded 1.0 for the fish samples that were not adjusted to account for a reduction in PCB concentration resulting from recommended fish preparation.

**Exhibit 23. Calculated Hazard Quotient (HQ) for 2012 Fish Tissue Data
Assuming a Fish Ingestion Rate of 42 g/day**

River Section	Fish Species	PCB Concentration 50% Reduction	Hazard Quotient 50% Reduction	PCB Concentration <u>No</u> Reduction	Hazard Quotient <u>No</u> Reduction
Spokane Arm	Largescale sucker (whole)	113.8	3.4	227.6	6.8
	Brown Trout (fillet)	33.3	1.0	66.6	2.0
	Rainbow Trout (fillet)	28.8	0.9	57.6	1.7
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	1.0	66	2.0
	Northern Pikeminnow (fillet)	25.9	0.8	51.8	1.6
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	3.8	252	7.6
	Mt whitefish (fillet)	81.6	2.4	163.2	4.9
	Northern Pikeminnow (fillet)	53	1.6	106	3.2
	Rainbow Trout (fillet)	43	1.3	86	2.6

RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	1.9	126	3.8
	Mt whitefish (fillet)	125	3.8	250	7.5
	Rainbow Trout (fillet)	49.3	1.5	98.6	3.0
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	2.3	150.2	4.5
	Northern Pikeminnow (fillet)	21.6	0.6	43.2	1.3
	Rainbow Trout (fillet)	29.9	0.9	59.8	1.8

Exhibit 24 shows the hazard quotient for PCB-contaminated fish for the 2012 DOH data assuming a fish ingestion rate of 64 g/day for both the 50% PCB concentration and the full PCB concentration. As this table shows, all HQ results exceeded 1.0.

**Exhibit 24. Calculated Hazard Quotient (HQ) for 2012 Fish Tissue Data
Assuming a Fish Ingestion Rate of 64 g/day**

River Section	Fish Species	PCB Concentration 50% Reduction	Hazard Quotient 50% Reduction	PCB Concentration <u>No</u> Reduction	Hazard Quotient <u>No</u> Reduction
Spokane Arm	Largescale sucker (whole)	113.8	5.2	227.6	10.4
	Brown Trout (fillet)	33.3	1.5	66.6	3.0
	Rainbow Trout (fillet)	28.8	1.3	57.6	2.6
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	1.5	66	3.0
	Northern Pikeminnow (fillet)	25.9	1.2	51.8	2.4
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	5.8	252	11.5
	Mt whitefish (fillet)	81.6	3.7	163.2	7.5
	Northern Pikeminnow (fillet)	53	2.4	106	4.8
	Rainbow Trout (fillet)	43	2.0	86	3.9
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	2.9	126	5.8
	Mt whitefish (fillet)	125	5.7	250	11.4

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	Rainbow Trout (fillet)	49.3	2.3	98.6	4.5
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	3.4	150.2	6.9
	Northern Pikeminnow (fillet)	21.6	1.0	43.2	2.0
	Rainbow Trout (fillet)	29.9	1.4	59.8	2.7

Exhibit 25 shows the cancer risk for PCB-contaminated fish based on the 2012 DOH data and assuming a fish ingestion rate of 42 g/day. All cancer risks exceed *de minimis* cancer risks, as well as the 1E-4 cancer risk threshold Dr. Keenan set as an acceptable risk.

Exhibit 25. Calculated Cancer Risk for 2012 Fish Tissue Data Assuming a Fish Ingestion Rate of 42 g/day

River Section	Fish Species	PCB Concentration 50% Reduction	Cancer Risk 50% Reduction	PCB Concentration <u>No</u> Reduction	Cancer Risk <u>No</u> Reduction
Spokane Arm	Largescale sucker (whole)	113.8	1.4E-04	227.6	2.7E-04
	Brown Trout (fillet)	33.3	4.0E-05	66.6	8.0E-05
	Rainbow Trout (fillet)	28.8	3.5E-05	57.6	6.9E-05
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	4.0E-05	66	7.9E-05
	Northern Pikeminnow (fillet)	25.9	3.1E-05	51.8	6.2E-05
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	1.5E-04	252	3.0E-04
	Mt whitefish (fillet)	81.6	9.8E-05	163.2	2.0E-04
	Northern Pikeminnow (fillet)	53	6.4E-05	106	1.3E-04
	Rainbow Trout (fillet)	43	5.2E-05	86	1.0E-04
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	7.6E-05	126	1.5E-04
	Mt whitefish (fillet)	125	1.5E-04	250	3.0E-04
	Rainbow Trout (fillet)	49.3	5.9E-05	98.6	1.2E-04
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	9.0E-05	150.2	1.8E-04
	Northern Pikeminnow (fillet)	21.6	2.6E-05	43.2	5.2E-05
	Rainbow Trout (fillet)	29.9	3.6E-05	59.8	7.2E-05

Exhibit 26 shows the cancer risk for PCB-contaminated fish based on the 2012 DOH data and assuming a fish ingestion rate of 64 g/day. As shown for the above calculations, all cancer risks exceed *de minimis* cancer risks, as well as the 1E-4 cancer risk threshold Dr. Keenan set as an acceptable risk.

**Exhibit 26. Calculated Cancer Risk for 2012 Fish Tissue Data Assuming a
Fish Ingestion Rate of 64 g/day**

River Section	Fish Species	PCB Concentration 50% Reduction	Cancer Risk	PCB Concentration No Reduction	Cancer Risk
Spokane Arm	Largescale sucker (whole)	113.8	2.1E-04	227.6	4.2E-04
	Brown Trout (fillet)	33.3	6.1E-05	66.6	1.2E-04
	Rainbow Trout (fillet)	28.8	5.3E-05	57.6	1.1E-04
RM 33.7 – Little Falls Pool	Largescale sucker (whole)	33	6.0E-05	66	1.2E-04
	Northern Pikeminnow (fillet)	25.9	4.7E-05	51.8	9.5E-05
RM 56.6-57.1 – Upper Lake Spokane	Largescale sucker (whole)	126	2.3E-04	252	4.6E-04
	Mt whitefish (fillet)	81.6	1.5E-04	163.2	3.0E-04
	Northern Pikeminnow (fillet)	53	9.7E-05	106	1.9E-04
	Rainbow Trout (fillet)	43	7.9E-05	86	1.6E-04
RM 64 & 77 – Nine Mile Dam Up River Dam	Largescale Sucker (whole)	63	1.2E-04	126	2.3E-04
	Mt whitefish (fillet)	125	2.3E-04	250	4.6E-04
	Rainbow Trout (fillet)	49.3	9.0E-05	98.6	1.8E-04
RM 84.4 & 96 – Upriver Dam to Border	Largescale Sucker (whole)	75.1	1.4E-04	150.2	2.7E-04
	Northern Pikeminnow (fillet)	21.6	3.9E-05	43.2	7.9E-05
	Rainbow Trout (fillet)	29.9	5.5E-05	59.8	1.1E-04

2. FISH CONSUMPTION RISKS AS DEFINED BY LAW ARE BASED ON THE *DE MINIMIS* CANCER RISK LEVEL 1E-6

Rebuttal to Dr. Keenan's statement that a cancer risk level of 1E-6 to 1E-4 is acceptable because it falls within EPA's acceptable risk range.

While I do agree with Dr. Keenan's statement, and he has correctly cited the U.S. EPA risk management framework (which is explained in the "Don Clay memo") [30]—which I have relied on for most of my 300 HHRA's—it is not applicable to this case. This is not an U.S. EPA-led site; there is no U.S. EPA remedy to be evaluated, so Dr. Keenan is citing a risk management framework that is not germane. As I discussed in great detail in Volume 3 of my expert report, DOH is the lead agency responsible for protecting the health of Spokane fish consumers. Furthermore, and perhaps more importantly, Dr. Keenan is ignoring the Washington State law that governs the acceptable risk for fish consumption. That law is the National Toxics Rule (NTR), which is overseen by Ecology: [31]

Washington State's water quality standards for toxic substances (WAC 173-201A-040[5]) define human health-based water quality criteria by referencing 40 CFR 131.36, also known as the National Toxics Rule (NTR). [31]

The NTR specifically considers fish consumption of contaminated fish to make a determination on whether Washington water bodies are meeting health-based standards:

The NTR criteria were issued by EPA to Washington State in 1992. These criteria are designed to minimize the risk of adverse effects occurring to humans from chronic (lifetime) exposure to toxic substances through the ingestion of drinking water and contaminated fish and shellfish obtained from surface waters. The NTR criteria are regulatory values used by Ecology for a number of different purposes, including permitting wastewater discharges and assessing when waterbodies are adversely impacted by contaminants. [31]

Most importantly, the NTR criteria are specifically based on a 1E-6 cancer risk level:

The NTR criteria values are based on a daily fish consumption rate of 6.5 grams/day and a risk level of 10⁻⁶...A risk level is an estimate of the number of cancer cases that could be caused by exposure to a specific contaminant. At a risk level of 10⁻⁶, one person in a million would be expected to contract cancer due to long-term exposure to a specific contaminant. [31]

Dr. Keenan has ignored the NTR criteria. In my experience, risk-based levels as defined by U.S. EPA and state laws trump or supersede the results of site-specific risk assessments (for example, when groundwater

risks are compared to chemical-specific Maximum Contaminant Levels [MCLs: defined in the Clean Drinking Water Act], MCLs are always used as the groundwater risk standard). That is, environmental laws or policies, which are referred to by U.S. EPA as Applicable or Relevant and Appropriate Requirements (ARARs) are usually given deference and weighted more heavily than the results of a risk assessment. Indeed, the U.S. EPA risk management framework Dr. Keenan cites (the Don Clay memo [30]) was specifically developed for Superfund sites—not fish consumptions advisories—states that ARARS need to be considered: [30]

Specifically, the following points are made in the memorandum:

Where the cumulative carcinogenic site risk to an individual based on reasonable maximum exposure for both current and future land use is less than 10(-4) and the non-carcinogenic hazard quotient is less than 1, action generally is not warranted unless there are adverse environmental impacts. However, if MCLs or non-zero MCLGs are exceeded, action generally is warranted. [30]

Indeed, ARARS are one of the two threshold criteria in the National Contingency Plan (NPL). [32]

As DOE states, exceedances of the risk-based values established in the NTR may trigger state enforcement action under the Clean Water Act (which is a Statute):

The NTR criteria are thresholds that, when exceeded, may lead to regulatory action. When water quality criteria are exceeded, the federal Clean Water Act requires that the waterbody be put on a list and that a water cleanup plan be developed for the pollutant causing the problem. This list is known as the 303(d) list, and the water cleanup plan results from a Total Maximum Daily Load (TMDL) study and public involvement process. Ecology uses the TMDL program to control sources of the particular pollutant in order to bring the waterbody back into compliance with the water quality standards.

Exhibit 27 lists the NTR screening fish tissue concentrations. Based on the 2012 Spokane fish sampling dataset, all fish samples exceed the NTR levels, even though these fish tissue PCB concentrations are based on a daily fish consumption rate of 6.5 grams/day.

Exhibit 27. National Toxics Rule Criteria, National Recommended Water Quality Criteria, and EPA Screening Values for the Protection of Human Health for Contaminants Detected in Fish Tissue, WSTMP 2004–2005 [21]

Analyte (ppb ww) ¹	National Toxics Rule	National Recommended Water Quality Criteria ²	EPA Screening Values			
			Subsistence Fishers		Recreational Fishers	
			Noncancer	Cancer	Noncancer	Cancer
Mercury	825	300	49	-	400	-
Total PCBs ³	5.3	2.0	9.83	2.45	80	20
2,3,7,8-TCDD ⁴	0.07	-	-	-	-	-
2,3,7,8-TCDD TEQ 4, 5	-	0.026	-	0.0315	-	0.256
4,4'-DDD	45	17	-	-	-	-
4,4'-DDE	32	12	-	-	-	-
4,4'-DDT	32	12	-	-	-	-
Total DDT ⁶	-	-	245	14.4	2000	117
Chlordane ⁷	8.3	11	245	14.0	2000	114
Aldrin	0.65	0.23	-	-	-	-
Alpha-BHC	1.7	0.64	-	-	-	-
Beta-BHC	6.0	2.2	-	-	-	-
Chlorpyrifos	-	-	147	-	1200	-
Chlorthal-Dimethyl (Dacthal)	-	-	-	-	-	-
Dieldrin	0.65	0.25	24	0.307	200	2.5
Endosulfan Sulfate	540	24000	-	-	-	-
Endrin	3200	230	147	-	1200	-
Heptachlor Epoxide	1.2	0.44	6.39	0.54	52	4.39
Hexachlorobenzene	6.7	2.5	393	3.07	3200	25.0
gamma-BHC (Lindane)	8.2	230	147	3.8	1200	30.7
Methoxychlor	-	-	-	-	-	-
Mirex	-	-	98	-	800	-
Pentachloroanisole	-	-	-	-	-	-
Toxaphene	9.8	3.7	122	4.46	1000	36.3
PBDEs	-	-	-	-	-	-

These NTR-derived PCB concentrations should not be considered conservative because a fish consumption rate of 6.5 g/day is far less than even the minimum fish consumption rate recommended by governmental health agencies of 32–48 g/day (8–12 ounces/week).[29] Moreover, DOH uses daily fish consumption rates of 59.7 and 175 g/day, which correspond to fish tissue PCB concentrations of 0.59 and 0.2 ppb, respectively (which are even less than the NTR PCB concentrations shown in Exhibit 27), which correspond to the *de minimis* cancer threshold.

DOE stresses that while it coordinates with DOH, it is DOH that is mandated with protecting public health: [21]

Most fish tissue contaminant data from Washington fish, regardless of who conducted the study, make their way to DOH for evaluation regarding the safety of consuming contaminated fish. The following is an overview of how Ecology and DOH evaluate fish tissue data to meet different needs.

Ecology's role is to determine whether water quality standards are met and to begin the process to correct problems where standards are not met. DOH and local health departments are responsible for developing fish consumption advisories in Washington. There is some overlap in these evaluations because the water quality standards that fish tissue data are compared to were developed for the protection of human health.

Washington's water quality standards criteria for toxic contaminants were issued to the state in EPA's 1992 National Toxics Rule (NTR) (40CFR131.36). The human health-based NTR criteria are designed to minimize the risk of effects occurring to humans from chronic (lifetime) exposure to substances through the ingestion of drinking water and consumption of fish obtained from surface waters. The NTR criteria, if met, will generally ensure that public health concerns do not arise, and that fish advisories are not needed.[21]

Exhibit 28 shows the *de minimus* fish tissue PCB concentrations DOH has derived for both cancer and noncancer health effects. The differences between *de minimis* values is due to the slightly different methodologies used by DOE and DOH. What is notable, however, is that neither DOH nor DOE apply the probabilistic HHRA methodology Dr. Keenan uses.

Exhibit 28. DOH *De Minimis* Fish Tissue PCB Concentrations [10]

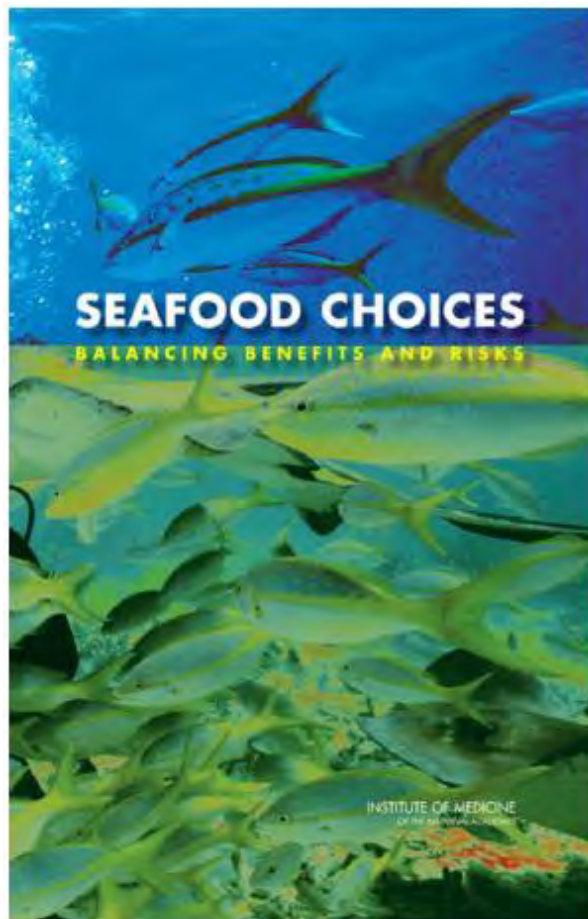
Fish Tissue Screening Levels (SL)				
Noncancer endpoint		Cancer endpoint		
$SL_{PCB\ Conc.} = \frac{RfD \times BW}{CR}$		$SL_{PCB\ Conc.} = \frac{ARL \times BW}{CSF \times CR}$		
Analyte	RfD Noncancer (mg/kg-day)	CSL Cancer (mg/kg-day) ¹	Tissue SL (59.7 gm/day) ppb	Tissue SL (175 gm/day) ppb
PCBs	0.00002		23	8
PCBs		2	0.59	0.2
PBDEs	0.0001		100	34
Mercury	0.0001		100	34

Considering the above information begs the question of why DOH does not default to the PCB fish tissue levels corresponding to either the NTR or DOH-derived PCB contaminant levels that would protect Spokane fish consumers from developing cancer? The answer is that DOH has adopted a public health approach that balances the benefits and risks of eating PCB-contaminated fish. As I discussed previously, although a diet rich in fish tissue is necessary to maintain optimal health, this comes at a cost of consuming toxic amounts of PCBs that cause noncancer and cancer health effects. Therefore, to minimize the PCB-toxicity and maximize the health benefits, DOH has little choice but to ignore the PCB cancer

risks. DOH has opted instead to focus on the health benefits and calculate fish consumption rates only on the noncancer effects. To do otherwise would effectively place a total ban on eating Spokane PCB-contaminated fish. While this is reasonable and widely accepted public health policy, it remains a fact that the PCB-contaminated fish are well above the *de minimis cancer* risk level.

DOH's health policy on dealing with PCB-contaminated fish to develop its fish consumption advisories follows the recommendations of the NASIOM guideline in its thoughtful and well-reasoned book, *NAS Seafood Choices: Balancing Benefits and Risks* (2007). [29] (See Exhibit 29.)

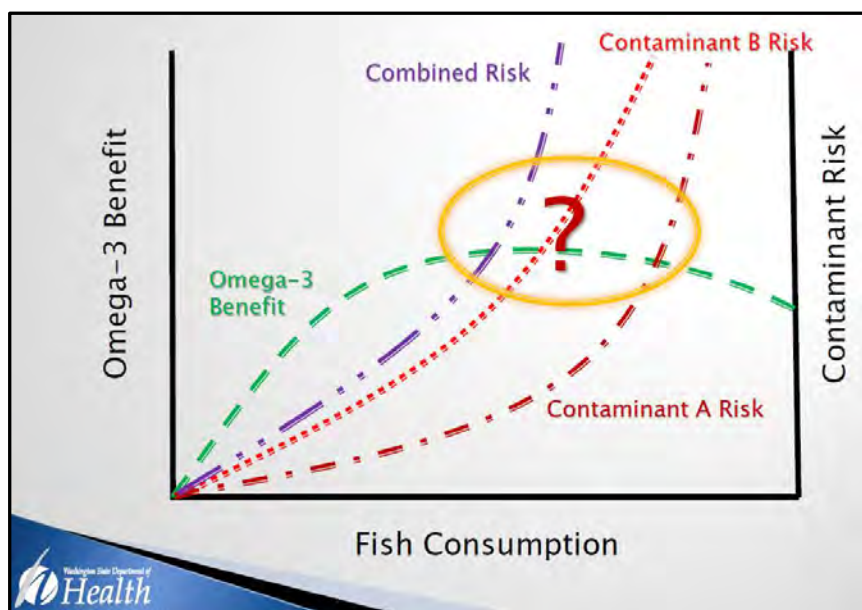
Exhibit 29. NAS Seafood Choices: Balancing Benefits and Risks (2007)



Although the NAS book provides an excellent overview of the toxicity of contaminants in fish and the health benefits of eating fish, it is largely qualitative, and its recommendations are fairly general. DOH has taken some of that information to make it somewhat quantitative, as shown in the schematic in

Exhibit 30. This graph shows a fish consumption dose-response curve with both the omega-3 benefits and contaminant health risks on the y-axis (on either side of the graph). Although the omega-3 benefits increase with increasing fish consumption, at a point there is no additional health benefit (and the omega-3 curve reaches a maximum level and levels off; this would be the point of maximum benefit). At the same time, with increasing fish consumption, the contaminant toxicity increases, exceeding the safe daily intake being. The maximum health-benefit *point* occurs when the omega 3-curve intersects with the toxic contaminant curves (there are two contaminants shown, and they have different toxicities). Although this schematic illustrates the concept, the single health-benefit point is difficult to actually quantify. However, the one fact that is obvious from this graph is that *if* DOH considered cancer as the toxic endpoint (which they do not), Spokane fish consumers would get no benefit from the health effects of a fish-rich diet because the recommended number of fish meals that would be safe to eat at *de minimis* cancer risk levels (based on the 2012 fish data) would be reduced by orders of magnitude.

Exhibit 30. DOH Graph Illustrating the Health-Benefit Analysis that Underlies Its Fish Consumption Advisories



This graph also shows that it is urgent that PCB levels in fish be reduced so that Spokane fish consumers can take full benefit of the nutritional advantages of an inexpensive source of fish oil containing omega 3. With every new medical study, more information shows just how beneficial fish are in preventing or

treating cardiovascular disease. For example, very recently (last week; December 13, 2019) FDA approved a new fish oil drug to reduce the likelihood of heart attacks and stroke: [33]

The U.S. Food and Drug Administration on Friday expanded the approved use of a fish-oil-derived drug to reduce the likelihood of heart attacks and strokes in high-risk patients.

The drug, Vascepa from Amarin Corp. PLC, now becomes a new tool for reducing the risk of heart attacks, strokes and deaths in millions of heart-disease or diabetes patients with elevated triglycerides while opening up a multibillion-dollar commercial opportunity for its maker. The expanded label could mean Vascepa sales surpass \$3 billion, analysts say. Last year's sales approached \$230 million.

Vascepa was approved in the U.S. in 2012 to treat adults with severe hypertriglyceridemia, or very high levels of triglycerides, which are fats that circulate in the blood. Since then, Amarin has been exploring whether the drug's effect goes further by reducing the risk of heart disease. [33]

As I have stated previously, the current levels of PCBs in Spokane fish prevent fish consumers from enjoying the benefit of a low-cost source of fish oil, and the City of Spokane's efforts to reduce PCB loading will have the greatest effect on reducing not only the toxicity of PCBs but increasing the overall well-established health benefits of a diet rich in fish tissue, particularly fish oil containing omega-3, heart-healthy fatty acids.

3. BACTERIA AND OTHER CONTAMINANTS DO NOT INTERFERE WITH FISH CONSUMPTION

This sections addresses the various references in Defendants' expert reports (Herman and Desvousges) to bacteria and other contaminants that do not affect fish consumption. There is no fish consumption advisory or other limit on the consumption of fish based on bacteria, algae blooms, phosphorous, dissolved oxygen, or various other contaminants cited in their reports (other than mercury, lead, PCBs, and PBDEs).

For the remainder of this section, I discuss contaminants related to sewage. In brief, my opinion is that sewage directly released into the Spokane River would have no impact on the health risks associated with eating PCB-contaminated fish.

Bacterial infections, illness, and disease associated with human exposure to pathogenic strains is a topic of interest to me and an area in which I have considerable expertise. I teach a graduate-level course in Environmental Epidemiology in which I lecture on the contagious transmission, vectors, and the damage

caused by toxins released by pathogenic bacteria. I cover many *waterborne* strains, including those that cause cholera (*Vibrio cholerae*; serogroup O1 or O139) and hemolytic uremic syndrome (HUS; *Escherichia coli*; the *E. Coli* H:O157 strain).

There has been no laboratory-confirmed case of cholera in the United States for many years; while sewage may be released into the Spokane River, cholera is of no concern. While there are many strains of *E. coli* (one of the most bountiful bacteria in our gastrointestinal microbiome), most are not pathogenic; some are even beneficial and produce vitamin K (which humans cannot synthesize and are necessary for blood clotting). However, some, such as *E. Coli* H:O157, can cause morbidity and death (particularly in children who develop HUS, which has a high mortality rate). Fortunately for humans, we do not harbor this strain but can be exposed via contact with animals. The major source of pathogenic *E. coli* is farm animals like cows, sheep, pigs, etc. What makes this strain so dangerous is that the infected animals are asymptomatic, so ranchers and farmers are never aware of this potentially deadly strain infecting their herd.

Bacteria are not transported through the fish skin so they would not contaminate the edible parts of the fish. Any pathogenic bacterial contamination of Spokane water would enter and be isolated in the fish gastrointestinal tract which is most often removed during the fish preparations stage, even when the fish is eaten whole.

It should also be noted that sewage has been shown to be effective in degrading PCBs. [34][35][36] For example, Mathews and Sithebe concluded: [22]

Pseudomonas aeruginosa, isolated from wastewater in the Notwane Sewage Treatment Plant was successfully used in biodegradation of recalcitrant polychlorinated biphenyls (PCBs). This having been successfully employed at the micro level, and further tests can be carried out to validate the results obtained in this study. With this recommendation in place, it is ideal to say that employing bacteria in the biodegradation processes of recalcitrant PCBs will be highly cost effective as it is a biotechnological process. [34]

In a study of PCBs in the Sheboygan Harbor, Michigan, Sonzogni states: [37]

Mono, di, and trihalobenzoates have been found to be completely mineralized to carbon dioxide and methane using bacteria from lake sediments and sewage sludge as well as enriched cultures grown on 3-chlorobenzoate (Suflita et al., 1982; Horowitz et al., 1983).

In summary, the bacteria from human waste in sewage does not create a health risk when eating fish from the Spokane River.

4. DR. KEENAN STATES THAT I MISREPRESENTED EXPOSURES TO MINORITY POPULATIONS

Dr. Keenan did not focus on minorities, ethnic groups, or those who fish out of need to supplement their diets. Due to concern about authorities inquiring about fishing, fish preparation, and consumption, many minorities do not participate in fishing surveys. This includes ethnic minorities and those who fish out of poverty. In some cases, there is a language barrier; in other cases, there is mistrust of authority figures. Whatever the reason, this group collectively is largely underrepresented in fish consumption surveys. This is supported by survey results collected by DOH, DOE and the SRHD, Assessment/Epidemiology Center. [23]

SRHD states in its 1998 report:

Barriers

Both cultural and language barriers inhibited the free exchange of information within both of the above focus groups. Cultural barriers included the inherent mistrust of public officials and the concept of focus groups as a method of research which would protect their anonymity. This latter cultural barrier was more apparent among the Russian community, however, the event took place in a naturally occurring and spontaneous setting in their church.

Representatives from both communities expressed concerns over the purpose of our questions. They wanted reassurance we were not inspectors or regulators there to get information that could incriminate them for fishing without a license. The Russian group seemed particularly concerned with the amount of information the facilitators had regarding the sources of metal contamination and the safety of the fish consumed from the Spokane River. [20]

The report emphasized that language barriers are often difficult to surmount:

The facilitators felt that the language barriers also contributed to their inability to fully explain the purpose and the process of the study. This may, in fact, be responsible for the low participation from the Laotian community and the low response rate from the translated surveys. [20]

It is also important to stress that some who fish the Spokane River do so for a good portion of their lives:

The respondents who fish the Spokane River reported the number of years they have fished the river. The range was 0 to 80 years. The mean for the number of reported years the river was fished by any one respondent is 13.51 years. [20]

The fish survey also showed that it is not the affluent who fish, but rather those with modest incomes. However, those in poverty or with low incomes may not have contributed to the survey data. The income breakdown for those who participated were reported in the following statements.

Survey Demographics

The most commonly reported income was \$40,000 to \$59,999 (60 respondents, 24.3%). Forty respondents reported their income as \$60,000 to \$79,999 (16.2%), followed by 25 respondents (12.0%) reporting their income as \$30,000 to \$39,999. [20]

Children are also likely underreported, and Dr. Keenan did not focus on this group in great detail. The survey reported that about 44% of the respondents had children, who likely shared in family fish meals.

Almost half of the respondents reported children in their household (44.1%, 109 households). The number of households with children who eat fish is 85. Adults eat fish in 232 of the respondents' households. [20]

It is also important to note that the Russian community reported eating a variety of fish, not just sport fish. These included bottom-feeding fish that have the highest PCB concentrations. Furthermore, they are not sport fishermen and do not catch and release their fish. They eat all of their catch or give it away to someone else who will eat it.

The locations attendees reported fishing were, the old Walk in the Wild Zoo, Upriver Dam, River Front Park, downtown area, T.J. Meenach Bridge, Nine Mile Bridge, and Long Lake. Attendees reported catching rainbow trout, German (brown) trout, suckers, catfish, crayfish, pike minnow, smallmouth bass, and perch from the river.

When asked what they do with the fish they catch (eat it, give it away, or release it) overwhelmingly they responded they either eat it or give it away. They only lose the fish "if it jumps off the hook or it is too small". [20]

Most importantly, the Russian Community does not follow the fish preparation advice from DOH. This has a significant impact on their health, as I previously discussed. If they eat the fish without cooking, they will exceed the fish consumption advisories by 2-fold for PCBs because the number of fish meals per month is based on a 50% reduction in PCB fish tissue levels. None of the reported fish preparation methods follow DOH guidance.

Respondents identified five ways in which they prepare the fish from the Spokane River to eat: cutlets (ground fish-cakes), fried, dried, fish soup, and pickled (herring). The cutlets are prepared by grinding the fish after removal of head and spine; the tiny bones are included in the cutlets. It was reported that a common method to prepare sucker fish to eat was to make cutlets with them. To dry the fish, respondents report, the fish are salted while raw and then dried; they are never cooked. The whole fish is used when it is dried excluding the intestines and the head. Fish soup is prepared in different ways. Some people use the head others do not. The herring is pickled fish

that is stored in a jar and does include bones. [18]

The survey results for the Laotian community put a fine point on my opinion that ethnic groups typically do not care to become actively involved in fish surveys (which has been my experience). Only six out of an estimated 200 in the community participated and provided information for the survey.

A total of six people participated in answering questions and entering into a discussion about the Spokane River and their fishing practices. General demographic information was uncovered at two meetings. The average family size for the Laotian community is four. It was estimated that the number of people in the Laotian community in Spokane County was approximately 200. [18]

Like the Russian community, members of the Laotian community eat what they catch and also eat bottom-feeding fish like catfish (discussed in Volume 3 of my expert report).

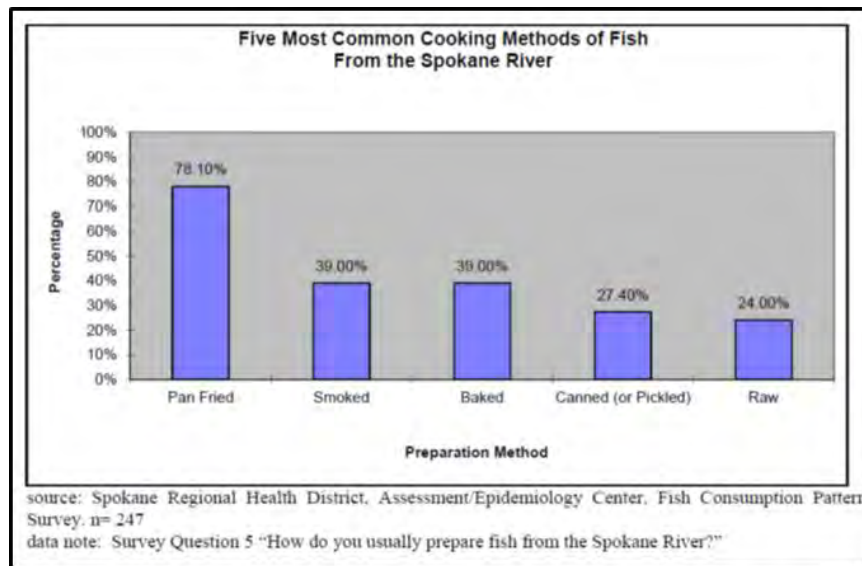
The fish that are caught from the river are generally used for consumption; they do not give them away. The attendees mentioned eating and knew of others to eat catfish, rainbow trout, perch, bass, walleye, and crawdads. [18]

They also described fish preparation methods that are inconsistent with the DOH-recommended practices since it appears that they do not cook the fish to decrease the fish oil. Rather, methods like barbecuing and broiling tend to retain the oil and may be why they prepare the fish in this manner.

The identified methods of preparing the fish to eat included frying, smoking, barbecuing, broiling, and in stews. They reported that the fish are always cleaned and gutted, they do not eat the bones, and always cut off the heads before preparing the fish to eat. [18]

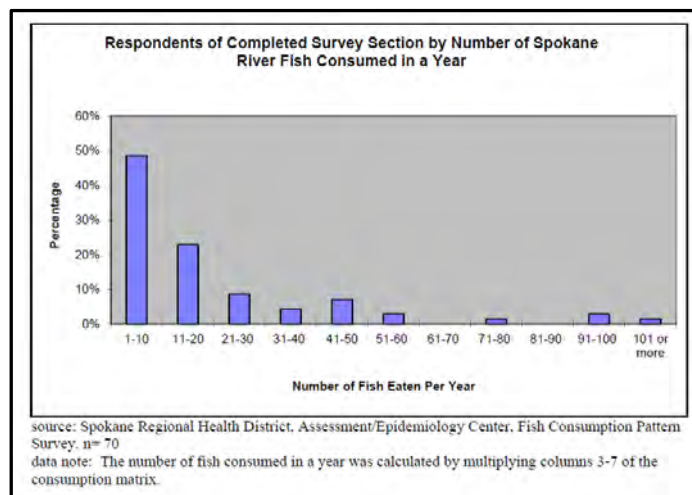
In fact, the number of fish respondents who do not pan fry their fish meal is considerable, showing a large portion of those surveyed may be exceeding the safe daily intake (RfD) of PCBs. (See Exhibit 31.)

Exhibit 31. Many Fish Consumers Do Not Pan Fry Their Fish to Remove the PCB-Containing Fish Oil [18]



As seen in Exhibit 32, approximately 5% of fish consumers (among those who participated in the survey) eat eight meals or more a month (96 meals per year), which is *not* safe for any fish species, according to the DOH Fish Consumption Advisories. It should also be noted that this survey was conducted in 1998, when the PCB levels were considerably higher than they are currently (2012); because PCBs are eliminated so slowly from the body, those consumers likely have significant PCB body-burden levels even today.

Exhibit 32. About 5% of Fish Consumers Reported Eating about eight Meals per Month [18]



Dr. Keenan relies heavily on fish consumption surveys but he does not acknowledge the significant uncertainty in the results and biases are very difficult to overcome. He seems to consider survey information a very accurate snapshot of real life. As was indicated in the 1998, weaknesses in fish consumption surveys [23] include those listed below and in Exhibit 33 and Exhibit 34. Many of the weaknesses of all of these fish survey methods will likely underrepresent ethnic groups

In addition to the 1998 SRHD report, a more recent 2013 DOH fish survey provides a very detailed analysis of Washington fish consumers and includes a long list of some of the uncertainties and bias in fish consumption surveys. [23]

For example, DOH notes that creel surveys only provide information on fishermen who were actively fishing that day. As shown in Exhibit 33, there are many weakness that could bias the study and under report those in poverty or in ethnic minorities. [23] Those include the following:

- Language barriers may exist between participants and interviewers;
- Survey results cannot be generalized to the entire population;
- May miss anglers if not all fishing locations and times are surveyed;
- May under- or overestimate yearly consumption if survey is not conducted throughout the year; and
- Anglers may not be as receptive to engaging in interviews as preselected personal interview survey interviewees.

Exhibit 33. Strengths and Weaknesses of Creel Surveys [23]

City of Spokane v Monsanto Co.
Expert Rebuttal Report of Richard L. DeGrandchamp, PhD, December 17, 2019

Table 9. Strengths and Weaknesses of Creel Surveys	
Strengths	Weaknesses
<ul style="list-style-type: none"> * Can assess site-specific consumption rates. * Can target specific at-risk populations who fish at contaminated sites. * The interviewer can observe the participant's fishing behaviors and catch as well as the condition of the interview site. * Recall bias is minimized by using visual aids and by having the interviewer refer to the fish caught around the time of the interview as a reference. * Results can be verified by looking at the daily catch of the participant. * Response rate is high. * More information can be gained by using visual aids and probing questions. * Creel surveys are routinely done for fishery management purposes; adding fish consumption questions to the surveys can be done with little added cost. 	<ul style="list-style-type: none"> * Only a limited number and types of questions are used to minimize survey time. * Language barriers may exist between participants and interviewers. * Surveys require well-trained staff that must be monitored for quality control. * If interviews are occurring at fishing sites, answers about consumption are hypothetical because the fish have not yet been consumed. * Participants who fish more frequently are more likely to be interviewed than those who fish less frequently.^a * Survey results cannot be generalized to the entire population. * May miss anglers if not all fishing locations and times are surveyed. * May under- or overestimate yearly consumption if survey is not conducted throughout the year. * Pilot testing for a target population is not as effective as is the case with personal interview surveys. * Anglers may not be as receptive to engaging in interviews as preselected personal interview survey interviewees. * Fears of contact with government officials may inhibit responses of minority groups. * Anglers in the field may not be as inclined or ready to respond as individuals that have been contacted and readied to participate in a personal interview survey. * Visual aids for unique seafood preparations are difficult to develop without knowledge of the target population. * If the water body is known to have chemical contamination, rates may be impacted by a suppression effect (i.e., the suppression of the harvest and consumption of fish), and hence may not result in protective risk estimates or cleanup levels. * It may difficult to know who actually consumes the fish.

a. Moya et al., 2008.

As shown in Exhibit 34, mail recall surveys also have many weaknesses and do not contain sufficient representation by minorities or those in poverty. [23] They include the following:

- Cannot reach people without mailing addresses;
- Higher number of inaccurate and incomplete responses; and
- May miss respondents who are illiterate, or have difficulty in understanding questions, or who cannot read the language.

Exhibit 34. Strengths and Weaknesses of Recall Mail Surveys [23]**Table 13. Strengths and Weaknesses of Recall Mail Surveys**

Strengths	Weaknesses
<ul style="list-style-type: none"> * Can assess region-specific consumption rates. * Can target and identify specific subpopulations of concern. * Least expensive since no interviewers are required. * Large numbers of respondents may be contacted over a large area. * Most likely to provide honest answers. * Complex technical data may be obtained if respondent takes the time to consider the questions and/or consult other sources. * Survey can cover broad areas of inquiry. 	<ul style="list-style-type: none"> * Cannot reach people without mailing addresses. * Questions must be carefully designed to compensate for lack of personal interaction. * Questions should be limited in scope and complexity. * Requires substantial follow-up efforts or incentives to achieve reasonable response rate. * Higher number of inaccurate and incomplete responses. * May miss respondents who are illiterate, or have difficulty in understanding questions, or who cannot read the language.

5. REBUTTAL TO DR. EATON'S OPINION

Dr. Eaton largely makes the same arguments against my opinion as he did in a previous lawsuit. I have attached my response to those issues here as **Appendix A**.

5.1. Rebuttal to Dr. Eaton's opinion on TCE Cancer Testing

Dr. Eaton states that, since trichloroethylene (TCE) was a widely used solvent that did not undergo cancer testing, that proves that industrial chemicals were not being tested for carcinogenicity during the period of 1930–1960. The fact that Dow did not perform any cancer test shows commercial chemicals were not being tested during that period. He states:

Examples of other industrial chemicals produced by other manufacturers tell the same story (i.e., no carcinogenicity testing was performed in the lack of the triggers outlined above). Dow and DuPont were primary producers of chlorinated solvents such as trichloroethylene (TCE) and perchloroethylene (PCE or tetrachloroethylene), widely used in a variety of industries, including the dry- cleaning industries (Doherty, 2000a, b). In spite of being widely used with high- levels of exposure because of their volatility, these chemicals were not tested for their carcinogenic potential by either Dow nor DuPont (or any of the other manufactures of TCE and PCE). Even though manufacture and use of TCE started in the early 1930s, neither the Hartwell 1951 nor the Shubik and Hartwell 1957 compendiums list any long- term feeding studies related to

trichloroethylene and TCE is not listed in the Hartwell 1941 compendium (Hartwell, 1941, 1951; Shubik and Hartwell, 1957). The first IARC Monograph on carcinogens, published in 1972, included entries for carbon tetrachloride and chloroform, but nothing on trichloroethylene (IARC and World Health Organization, 1972). An early review of TCE toxicity was provided by Shubik and Hartwell (1957). Numerous acute and subchronic studies of TCE were cited, including subchronic exposures at Dow chemical company laboratories Adams et al. (1951) as cited by Shubik and Hartwell (1957). But Dow never performed a 2- year chronic bioassay on TCE.

Dr. Eaton is simply stating because one chemical (a widely used solvent) out of thousands that were manufactured during 1930–1960 was not tested for cancer, there was no reason that PCBs should have been tested for carcinogenicity. Dr. Eaton is arguing a point that I did not cite as a reason or trigger for why Monsanto should have tested PCBs for cancer. Although PCBs were produced in massive quantities and released into the environment, I did not state that PCBs should have been tested because of that reason. The fact is, there were no triggers for anyone to be concerned about TCE during that period, and there were multiple reasons I cited and discussed in my expert report. But before I repeat my rationale for cancer testing, I should point out some interesting contradictory facts about the above quote by Dr. Eaton that do not support his opinion.

First, it is interesting to note that Dr. Eaton states that Dow conducted acute and subchronic testing on TCE:

Numerous acute and subchronic studies of TCE were cited, including subchronic exposures at Dow chemical company laboratories Adams et al. (1951)

This is in stark contrast to Monsanto's lack of concern about the toxicity testing of PCBs. As I stated in my expert report, Monsanto started PCB production in 1929, but conducted no toxicity tests on PCBs until 1969. Although Drinker, Miller, and others had conducted toxicity tests that showed high toxicity and precancerous evidence of tumors, Monsanto did not conduct such tests. [38] [39] The company did not perform any testing on PCBs until the IBT studies were started in 1969, and those were *prompted* not out of Monsanto concern about the toxicity but because the company admitted it had no toxicity data; furthermore, reports started to become publically available by 1969 that provided evidence that PCBs could be a worldwide contaminant. [40]

First, Dr. Eaton states that TCE was widely used and was volatile:

In spite of being widely used with high- levels of exposure because of their volatility, these chemicals were not tested for their carcinogenic potential by either Dow nor DuPont (or any of the other manufactures of TCE and PCE).

One of the reasons TCE would not be a good candidate for cancer testing is because it is volatile and is physically on the opposite side of the spectrum with regard to its physicochemical properties compared with PCBs. In this regard, Dr. Eaton is comparing two different classes of chemicals. The reason PCBs should have been tested is because they are not volatile, and the primary exposure route is ingestion. Because TCE is inhaled, there was no concern about exposure to the general public. By contrast, PCBs posed a great health threat because they are not volatile (i.e., are persistent), which is why they constitute a worldwide contaminant even today. Furthermore, TCE is not bioaccumulative and stored in human fat tissue for decades like PCBs are. Even though PCBs were banned in 1979, nearly all Americans still have detectable body burdens of PCBs. TCE, by contrast, is very rapidly eliminated from the human body within hours. For example, ATSDR states:

A relatively small amount of absorbed TCE is exhaled unchanged; most of an absorbed dose is metabolized and excreted in the urine.

After exposure to air concentrations between 50 and 380 ppm, approximately 58% of an absorbed dose appears in urine as metabolites (Monster, Boersma et al. 1976; Monster, Boersma et al. 1979). The time between TCE inhalation and urinary excretion of trichloroethanol is relatively short (biologic half-life approximately 10 hours) compared with the urinary excretion of trichloroacetic acid (biologic half-life approximately 52 hours). [41]

As I discussed in my expert report, one of the triggers was PCBs' similarity to dichloro-diphenyl-trichloroethane (DDT). During the 1940s, Monsanto was producing both DDT and PCBs, and the FDA showed DDT was carcinogenic: [4]

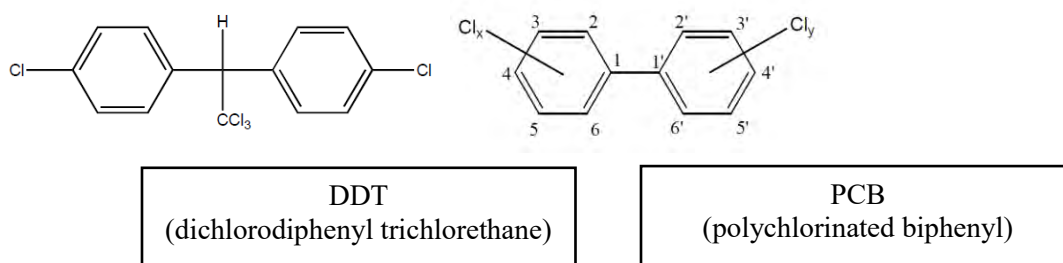
Tendency to hepatic tumor formation was, on the basis of comparison with many hundreds of rats of similar age, definite but minimal in both two-year series. Altogether, in both experiments, 4 rats each had one or more small hepatic cell tumors, from 5 to 12 mm. in diameter, paler than the surrounding liver tissue on gross examination, not sharply circumscribed microscopically, and composed of cells larger than those in the rest of the liver. Lobular architecture was almost obliterated. Mitoses were not noted. Some cells had foamy cytoplasm; some cells showed DDT changes of a degree greater than that elsewhere. Tumors of this type are not a sharply defined entity, and the question of their nomenclature cannot be treated here. They would probably be generally called adenomas because of their relative size, discrete gross appearance, and almost total loss of lobular architecture. There might be almost as much justification for considering them low grade hepatic cell carcinomas.

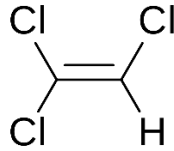
Eleven other rats showed varying amounts of nodular adenomatoid hyperplasia; the nodules were generally of 1 to 3 mm. diameter, and were usually noted grossly as scattered yellowish foci. Nodules smaller or less distinct microscopically were not diagnosed as adenomatoid hyperplasia. The microscopic appearance was essentially the same as in the larger tumor masses; difference in size is chiefly responsible for the difference in terminology. Nodular adenomatoid hyperplasia is almost never seen in our rat livers except after treatment with a few distinctly tumorigenic substances. About 1% of our older rats will spon-

What prompted FDA to begin its chronic cancer testing was DDT's accumulation and storage in body fat for long periods of time. [4] The FDA study showed that DDT was carcinogenic, and Monsanto already knew that PCBs and DDT shared the same physical properties (fat soluble) and were similar chemically. TCE is very dissimilar to either PCB or DDT because it does not share the same physical or chemical properties as either DDT or PCBs. It does not have either a phenyl ring or a benzene ring, which were chemical triggers for conducting cancer tests based on the structure-activity relationship.

PCBs and DDT share the same chemical properties as shown below and would be expected to show the same toxicity and carcinogenicity (the structure-activity relationship), whereas TCE does not share any of the properties that were known to be carcinogenic.

Exhibit 35. TCE Does not share the same chemical structures with PCBs and DDT Add an Exhibit heading and reference





TCE
Trichloroethylene

The other triggering evidence included specific pathological findings by Drinker [38] and Miller [39] that were known at the time to be preneoplastic lesions that form during the early stage of tumorigenesis and were seen at about 3.5 months. The pathological features or hallmarks of early tumorigenesis that were described by Drinker, as well as by Miller, included the following:

- Hyaline inclusions or bodies
- Mitotic figures
- Granulated cells

Despite these pathological hallmarks being identified and characterized as highly unusual, Monsanto conducted no chronic toxicity testing until 1969, when it began chronic studies. The very first cancer study conducted by Monsanto showed PCBs were carcinogenic. [42]

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1. INTRODUCTION

I have reviewed Dr. Eaton's Expert Report in this matter. The following summarize my rebuttal opinions. I have concluded Dr. Eaton:

1. Presents numerous tables and text from polychlorinated biphenyl (PCB) cancer studies that were produced to contain false information and data, even though Monsanto admitted in 1981 that they were false and invalid;
2. Relies on numerous false and fraudulent studies to make false statements and form his conclusions about the carcinogenicity of PCBs;
3. Incorrectly states the number of positive animal tests showing cancer based on discredited histopathological diagnostic criteria developed by the National Cancer Institute (NCI) in 1975 to incorrectly conclude the number of studies showing PCBs were carcinogenic;
4. Ignores the gold standard toxicology test results on PCBs that were published by the Public Health Service in 1944;
5. Presents an incorrect and misleading framework for the generally accepted toxicology practice used to develop scientific methods of testing and protocols;
6. Incorrectly states that there were no standard practices for conducting toxicity tests until after 1970;
7. Lists and discusses the important toxicological testing criteria pre-1970 and post-1970, and all but one are incorrect due to an incomplete knowledge of historical toxicity testing;
8. Does not cite or discuss the most important milestone in the field of toxicology: the 1949 U.S. Food and Drug Administration (FDA) "Black Book" written by Lehman et al. that presents standard toxicity testing protocols developed specifically for the chemical industry to assess chemicals that could potentially contaminate food;¹

9. Incorrectly states there were no “standard practices” developed before 1970 that could be used to test Monsanto’s PCBs when, in fact, standards were available in 1949 and were specifically designed for industrial chemicals like PCBs that were being produced in massive quantities and could be released into the environment;
10. Does not consider or even acknowledge the early industrial cancer studies that were being conducted in the late 1930s by Dow, DuPont, and Bayer AG; and
11. States that there were no good standard protocols for cancer testing before 1970, but ignores the FDA cancer study for dichlorodiphenyltrichloroethane (DDT) published by Fitzhugh and Nelson in 1947 that showed DDT was carcinogenic;² the study presented an excellent protocol that Monsanto could have easily adopted to test PCBs, and Monsanto likely knew about this study since it started producing PCBs in 1944.

2. GENERAL COMMENTS: DR. EATON’S ASSERTIONS REGARDING “STANDARDIZED PRACTICES” AND CANCER TESTING PROTOCOLS

Dr. Eaton states that there were no “standardized” toxicity testing protocols prior to 1970; this was, presumably, his explanation for why Monsanto could not have performed chronic toxicity and cancer testing prior to 1970. The evidence upon which Dr. Eaton relies is provided in summary format in Table 12 of his expert report. In that table, Dr. Eaton incorrectly states that there were no specific standard practices for numerous study design parameters and criteria needed to conduct cancer testing pre-1970. He juxtaposed pre-1970 practices with post-1970 practices in that table and for each ad hoc criterion (there are many more he ignores), he essentially states that there were no standard criteria pre-1970. While the study criteria Dr. Eaton bases his opinion on are vitally important to planning and implementing a rigorous study design, there are others that were ignored. Nevertheless, Dr. Eaton has used this comparison to support his opinion that there were few, if any, experimental standard practices for any of his categories prior to 1970 and, accordingly, I have focused on the criteria he has identified.

3. STANDARDS OF PRACTICE

On page 72, Dr. Eaton describes the history of industrial toxicology and cancer testing. His description is largely based on a single source—a textbook chapter by Henry F. Smyth, Jr., in *Casarett and Doull's Toxicology: The Basic Science of Poisons*.³ He does not state his process of review and analysis of historical studies or whether he even read the actual published studies from the 1900s to the 1950s. However, I am very familiar with the textbook he cites because it was the textbook I was trained with and it was *the* assigned textbook to me when I took my introductory toxicology course. It is now the very same textbook I assign to my students in the toxicology course I teach. While this textbook serves to provide an excellent *general overview* of specific topics in toxicology; it does not in any way provide a detailed historical treatise on the history of cancer testing. In other words, it is a general introductory textbook used in first-year toxicology courses that rather superficially touches on many aspects of the field of toxicology. Moreover, Dr. Eaton provides a single quote from the Smyth chapter as his major reference reliance document to suggest that cancer testing was not conducted in the early 1930s–1950s. This is incorrect and, as I have stated in my expert report, even major industrial chemical companies like Dow, DuPont and Bayer AG (which now owns Monsanto Company) were testing their products in the late 1930s to determine if they were carcinogens.

In contrast to Dr. Eaton's review of a single textbook, I have now collected and reviewed more than 200 original peer-reviewed reports on myriad aspects of cancer research. These reports involve early testing of laboratory animals starting in the late 1800s and continuing through the early 1970s. (I have been engaged in this research for over 5 years, and it forms the basis of my toxicology teaching materials.)

Based on my research and an analysis of Dr. Eaton's opinions regarding historical cancer testing, I find his opinion is biased, truncated, and a work of revisionist history, since cancer testing began much earlier than the 1970s, as did protocols underpinning such testing.

The term *standardized testing* also has a specific meaning in toxicology because it indicates that scientists and regulators are following the same procedures in order to comply with some new law or regulation that allows government scientists to compare different studies with the same

metrics. In this sense, standardization is intended to provide consistency. For chemicals that are regulated, the chemical industry must test them. However, starting in the late 1930s chemical companies were testing for carcinogenicity because they believed they had an obligation to protect both workers and the general public—not because they were required to.

It is not clear from Dr. Eaton's expert opinion, but he seems to indicate that cancer studies performed prior to 1970 are not valid or scientifically tenable. He also seems to indicate that Monsanto could not conduct cancer studies before 1970, suggesting that Monsanto was waiting for toxicologists to take the lead on standardization—and only then could Monsanto consider conducting its first cancer study in 1969. The evidence I have reviewed does not support his opinion.

Dr. Eaton states that, prior to 1970, animal cancer tests were somehow unreliable. He contrasts animal cancer testing protocols during the periods before and after 1970, stating:

In evaluating the state of science and how cancer testing has evolved since the 1930s, it is important to compare the state of animal cancer testing before and after standardized protocols came to fruition in the 1970s. Certain aspects of study design scientists take for granted today were not regarded as important in the 1930s. Table 12 lists these differences, which include treating the controls in the same fashion as treated animals, understanding the background incidence of disease in the studied experimental animal, and consideration of the age of animals tested, using an adequate number of animals to see a response, testing the animals for long enough periods of time (2 years), as well as numerous issues related to animal care and housing.

Dr. Eaton's Table 12 is presented in Exhibit 1 (I discuss this table at length in following sections).

Exhibit 1. Table 12 from Dr. Eaton Report

Table 12. Animal cancer testing study design practices before and after 1970

Study Design Parameters	Pre-1970 Practices	Post-1970 Practices
Number of Dose Groups	Typically a single dose group	Minimum of three or more groups
Method of Administration (e.g., Dermal, Inhalation, Gavage, Dietary)	Dermal or inhalation exposure (assess occupational exposure)	Dietary or gavage to ensure dose
Length of Administration (How Long)	Variable	Established period of time: Lifetime ~ 2 yrs
Animal Care	Not standardized	Rigidly controlled, standardized animal medicine practices
Tissue analysis	No uniform classification system	Established classifications
Pathology review	Single pathologist	Multiple pathologists
Statistical practices	None or non-standardized	Highly standardized
Group Size	Variable	Larger numbers of animals, animals individually tracked and assessed
Species	Multiple species	Rats or mice, consistent strain or sensitive strain
Gender	Random gender selection	Both genders or most sensitive gender
Age	Varied	Studies begin at specific, young ages
Historical Controls (Summary of Control Animals)	Generally not available	An integral part of study design
Doses Administered (Total Dose and Variability Within Study Period)	May have relied on a minimum range finding study (dose could be adjusted during study)	Use of a subchronic study to set chronic dose levels (doses aren't typically adjusted)
Observations	Limited	Comprehensive
Intervals of Administration (On/Off)	Variable intervals	Continuous
Test Substance	Purity impossible to determine	Purity confirmed, contaminants identified
Source of Test Compound	Not specified	Well documented
Record Keeping	No requirements	Good Laboratory Practice (GLP) regulations
Additional Analysis (e.g., Hematology, Urinalysis)	Limited	Comprehensive analyses
Laboratory Design	Not standardized	Clean/dirty corridor systems and Standard Operating Procedures
Study Segregation	Not standardized	One study per room

Source: Eaton 2019.⁴

Dr. Eaton's table indicates a belief that cancer studies in the 1930s through the 1960s were poorly designed. It is apparent that he has not actually reviewed those studies, because many of

the carcinogens we know today were first identified as carcinogens in that period. While cancer testing protocols have improved, clearly the early cancer studies achieved what they were designed to do: identify chemical carcinogens. Nevertheless, Dr. Eaton states Monsanto could not have identified PCBs as carcinogenic prior to 1970. I have reviewed and considered his evidence and supporting rationale; I have concluded the following:

1. Dr. Eaton ignores the sole intent and purpose of using laboratory animals in cancer testing and misrepresents the concept of standardized animal cancer testing protocols as they apply to Monsanto's Aroclors.
2. Dr. Eaton incorrectly states that cancer testing standardization occurred only after 1970, even though the FDA began standardizing animal cancer testing in 1947.²
3. Dr. Eaton ignores the fact that (with few exceptions) hundreds of chemical carcinogens were first identified in the 1930s and 1940s with animal cancer studies and that those studies have been reaffirmed and shown to be valid to this day.
4. Dr. Eaton ignores the fact that the most widely studied group of chemical compounds selected for animal cancer testing in the 1930s and 1940s were the very same chemical compounds that were, and continue to serve as, the feedstock for all organic compounds produced in the chemical industry. All organic chemical compounds start from coal tar, petroleum, and oil.
5. Dr. Eaton ignores the fact that standardization was actually a deliberate step to ensure a particular chemical carcinogen did not slip through the cracks of testing and to guard against a false negative study in which a chemical carcinogen would be incorrectly and falsely regarded as a noncarcinogenic. For example, the number of animals that are used in cancer studies must be increased for weak carcinogens compared to strong carcinogen. PCB carcinogenicity did not require hundreds of animals because it is not a very weak carcinogen.
6. Dr. Eaton does not cite any regulatory or well-established protocol(s) that he defines as a standard animal testing protocol developed in 1970.

7. Dr. Eaton ignored the fact that even Industrial BIO-TEST Laboratories, Inc. (IBT) (the contract laboratory that Monsanto hired to conduct its PCB cancer studies) did not follow any cancer testing protocol, so even under Dr. Eaton's theory, IBT's studies should not be considered as valid studies; IBT certainly did not adhere to Dr. Eaton's standard cancer testing practices in the early 1970s.
8. IBT knowingly included false and fabricated information and data in its cancer studies to make it appear PCBs were less toxic and carcinogenic than they actually were, and it submitted those false reports to Monsanto. Monsanto, in turn, submitted those fraudulent findings to U.S. EPA, the National Cancer Institute (NCI), and other scientific experts who reviewed the animal histopathology, cancer incidence rates, and other critical information important for making interpretative conclusions about the carcinogenicity of PCBs.
9. Dr. Eaton ignores the fact that, despite his conclusion that no standardized cancer testing protocols were available until the 1970s, major industrial chemical companies like Dow, DuPont, and Bayer AG were screening their chemical compounds for carcinogenicity using animal cancer tests by the late 1930s to protect both their workers and the general public.
10. Dr. Eaton fails to note that an excellent and robust animal cancer standard study design had been developed by the FDA by 1943 (published in 1947 by Fitzhugh and Nelson) when it started its DDT cancer study.² This study design performed as it was intended because the FDA was able to show that DDT was a carcinogen in 1947. This study was conducted more than 20 years before 1970. FDA was able to correctly conclude DDT was carcinogenic based on the generally accepted practice of applying the cancer testing protocols used in the more than 1,000 studies published by that time. The FDA's findings and conclusions have stood the test of time, and many laboratories duplicated FDA's findings and confirmed DDT is carcinogenic.
11. I have reviewed the general study design IBT implemented in 1971 cancer studies, and it was no different from the design of cancer studies that were being performed in the 1930s and 1940s. These studies were not in any way complex or sophisticated, and they required no specialized equipment or analyses that would have prevented Monsanto from conducting the same studies decades earlier. Monsanto could have performed similar cancer studies

on Aroclors in the late 1930s and 1940s. Had Monsanto conducted the tests decades earlier, I believe they would have concluded PCBs were carcinogenic.

12. Dr. Eaton has not considered that if Monsanto had simply followed the very same cancer testing protocol used by the FDA in its 1947 DDT cancer study, it would have determined that PCBs were also carcinogenic.²

The sole intent of long-term animal cancer studies for industrial chemicals like PCBs (that are not regulated) is to determine if they are carcinogenic. It should be stressed that *all* animal tests are designed to *screen* compounds to determine if they are carcinogenic in *animals*. Animal studies provide supporting evidence that a chemical is a human carcinogenic. We cannot perform cancer testing on humans because it is unethical to expose humans to compounds that could be carcinogenic. Therefore, it is universally accepted by toxicologists that we must screen them *before* humans are exposed and not *after* the fact. Dr. Eaton suggests that the chemical industry waited until *after* humans were exposed (whether in the workplace or general public) and that those human exposures must have produced observable human cancers before the chemical industry would perform a long-term animal cancer test. It defies logic to suggest we would test a chemical compound in rats if we already knew that the compound produced cancer in humans.

It is also important not to superimpose the current state-of-the-art in cancer testing protocols toxicologists currently use and assume cancer experts in the 1930s–1960s were ignorant, naïve, and/or untrained; to suggest otherwise is scientific hubris. Many of the compounds we know today as carcinogens were first identified in the 1930s–1960s.

It is clear that Dr. Eaton has ignored many of the early and excellent cancer studies that form the basis of our current understanding of carcinogenicity because they were not conducted under what he considers standardized protocols or methods. He tends to focus on the exceptions and not the rule.

With rare exceptions, the vast majority of chemical compounds found to be carcinogenic in the early 1930s and 1940s are still today regarded as carcinogenic. This shows that the gradual refinement of cancer testing codified in Dr. Eaton's standardization paradigm is unrelated to the goal of animal cancer testing—which is to simply test whether a chemical compound is carcinogenic.

For example, the very first animal cancer test was performed in 1915 by Yamigawa and Ichikawa when they applied coal tar to rabbit ears.⁵ With prolonged exposure, cancerous growths developed, demonstrating that chemical compounds could be tested in animals. This experimental protocol sounds crude by today's standards, but it could be repeated in any university laboratory by first-year toxicology students, yielding the same results and with only a few rabbits. They did not need a standard practice protocol and their experimental design proved to be excellent for their goal and purpose. Likewise, Monsanto did not need to use thousands of animals with sophisticated expensive equipment to identify PCB as carcinogens in the 1930s and 1940s, and any qualified academic institution during that time would be well-equipped to conduct the same cancer experiment IBT conducted in the early 1970s.

As I discussed in my expert report, the sole opinion I have expressed in my report regarding historical animal cancer testing is simple: Monsanto *could have* and *should have* conducted long-term animal cancer tests in the 1930s or 1940s. The issue of when cancer testing protocols were standardized is not relevant to my opinion because the definition of standardized cancer testing is constantly evolving and being refined. Toxicologists are today relying on much more sophisticated study designs than were used by cancer experts conducting studies in 1970–1990, but that does not make the earlier studies any less relevant or wrong.

For example, Dr. Eaton presents his loose definition of a standard animal cancer testing protocol (for which he cites no reference), but fails to mention the gold standard of cancer testing developed by the leading governmental toxicology agency in the U.S.—the National Toxicology Program (NTP).⁶ The NTP protocol is far more sophisticated, complex, and lengthy than Dr. Eaton's ad hoc standard protocol. The NTP protocol is extremely sophisticated, requiring many different experts from many different scientific disciplines and requires *far more* animals than Dr. Eaton's standard criteria indicate. But experiments following this protocol are extremely expensive, long, and labor-intensive to conduct. However, the NTP studies are based on the most rigorous cancer testing protocols and their findings are regarded as the gold standard among most toxicologists in the United States and around the world. The NTP is the only governmental group charged by the U.S. Congress to produce a yearly compendium identifying chemical cancer compounds. The NTP summarizes the *Report on Carcinogens* as follows (<https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html>):

The Report on Carcinogens (RoC) is a congressionally mandated, science-based public health report that identifies agents, substances, mixtures, or exposure circumstances (collectively called "substances") in our environment that pose a hazard to humans.

The NTP was established in 1978 to:

- Coordinate toxicology testing programs within the federal government;
- Strengthen the science base in toxicology;
- Develop and validate improved testing methods.
- Provide information about potentially toxic substances to health, regulatory, and research agencies, scientific and medical communities, and the public.

The NTP standard protocol is perhaps the most detailed and rigorous that has been developed to date.⁶ The reason the NTP cancer study standard protocol is important to my rebuttal opinion is because each *individual* cancer study requires more than 800 laboratory animals and was estimated to cost \$2–\$4 million in 2009. Obviously, these expensive and sophisticated protocols preclude most industrial and university laboratories from following the NTP cancer testing protocol. Nonetheless, many toxicologists in both academia and industry perform many cancer studies each year that are accepted in the scientific community and add valuable data and information to the catalog of identified carcinogens *yet do not follow* the NTP protocol because it would be impossible. Applying Dr. Eaton's reasoning about the importance of standardizing cancer testing protocols, all cancer testing prior to the protocol used by NTP today would be considered substandard and flawed, and the results therefore suspect, because it did not follow the most current standard protocol.

Regarding the supposed lack of a standardized approach prior to 1970, Dr. Eaton makes contradictory statements about *why* Monsanto did not conduct animal cancer studies in the 1930s, 1940s, 1950s, and 1960s. While Dr. Eaton states that standardized toxicological testing only occurred after 1970, he does not mention that standardization of any toxicology testing occurs as a result of a new law or regulation that chemical companies must satisfy. That is,

testing protocols are not standardized because the government suddenly decides that it would be a good idea. Standardized toxicological testing protocols are developed first by the government to meet the requirements of a proposed or new law or regulation. For example, the FDA first published guidance for the chemical industry to assess the toxicity of chemicals in food in 1949 (Lehman et al.); the guidance is known as the Black Book.¹ This guidance was developed in response to the 1938 FD&C act. Although the FDA had no legal authority to force the chemical industry to follow its guidance, the Agency thought it important to provide standardized testing protocols for those in the chemical industry who were planning to add chemicals to food or thought that, due to the amounts they were producing, their chemicals *could* contaminate food (PCBs fall in this latter category).

The importance of impending or new laws or regulations that force the government to standardize toxicological testing cannot be overemphasized with regard to Dr. Eaton's opinion because it specifically addresses a need by the government—not by academic or industrial cancer researchers. The point at which the government standardizes testing does not indicate that, prior to that point, scientific cancer experts were conducting cancer studies on chemicals in a random ad hoc fashion; it simply marks a point in time when the government instructs the chemical industry on how it should conduct experiments to *satisfy new or anticipated laws*. In this sense, new standards are government instructions that apply to laws or regulation. Furthermore, the FDA did not create standards in a vacuum; it was aware of the more than 1,000 cancer studies that had been published in peer-reviewed scientific journals by the 1950s, and those studies provided a road map of generally accepted practice at the time.

Dr. Eaton's opinion regarding the importance of a standardized protocol is contradictory. He acknowledges that Monsanto began performing cancer tests in 1969, yet then says that a company would have had no standardized testing protocols to conform to until years after that time.

I have reviewed dozens of Monsanto memos, reports, and documents pertaining to the company's toxicological testing; none of them state or even suggest that the reason Monsanto waited until 1969 to start testing PCBs for carcinogenicity was because a standardized methodology was unavailable before that time. At the very least, Monsanto must have known by

1947 that scientifically tenable cancer testing protocols had been developed for industrial chemicals because that was when FDA (Fitzhugh and Nelson, 1947) published its findings showing one of Monsanto's products (DDT) was carcinogenic in animals. ²

The standards Dr. Eaton is suggesting were available only post-1970 would have had little impact on identifying carcinogens like PCBs and DDT. In fact, FDA's 1947 study showing DDT was carcinogenic should be proof that cancer studies performed at that time were sufficiently powerful to reveal PCB – a similar compound -- was carcinogenic. ²

3.1. Dr. Eaton incorrectly states that “standardized” cancer testing protocols were only available after 1970

Dr. Eaton did not cite, discuss, or consider for his opinion the most important historic milestone in toxicity testing: The 1949 FDA Black Book.¹ It is hard to overstate the importance of this FDA guidance document, since it was prepared for the chemical industry to use in designing a series of robust toxicological tests of the products chemical companies were producing. It represents the overall approach and experimental paradigm that academic and industrial toxicologists use to test all chemical compounds. It is the foundation of toxicological testing that toxicologists still use today. The fact that Dr. Eaton does not even *cite* this document appears to be an indication that his review of historical toxicity testing is superficial. In the sections below, I present the salient aspects of these original standardized and comprehensive testing protocols because Dr. Eaton did not do so. That is, he did not present a discussion of this document, and that failure is the impetus for including the following facts and information.

3.1.1. Overview of the FDA Black Book

Starting in 1938, with the passage of the FD&C, the FDA was the lead regulatory agency that oversaw applications for, and safety of, new drugs. The FD&C recommended the chemical industry to perform toxicity tests on any new drugs prior to being sold. The FDA developed general guidelines for the industry, but there were no designated standards.

The first toxicity testing standards were developed by the FDA in 1949 as part of the implementation of the FD&C.¹ The standards called for a battery of toxicity tests that the

chemical industry should conduct. This was the first comprehensive testing framework to be issued as a guidance document for the chemical industry, and it was intended to be used by the entire chemical industry. This guidance is referred to as the Black Book. The protocols are detailed in the article Procedures for the Appraisal of the Toxicity of Chemicals in Foods (Lehman, 1949). The protocols presented in this document were prepared by the some of the leading scientists of the day, including Drs. Lehman, Laug, Woodard, Draize, Fitzhugh, and Nelson, who were all FDA scientists and were experts in their fields. The protocols are detailed in sections on: (1) chemistry, (2) acute toxicity, mechanism and site of action, (3) allergic responses, (4) subacute and chronic toxicity, reproduction and paired feeding studies, (5) biochemistry, and (6) pathology. Although these topics were finally standardized by the FDA in 1949, these protocols represented the state-of-the-science that scientists were following in the early 1940s. They represented the cumulated scientific methods that were being used as generally accepted practice in toxicology well before 1949.

3.1.2. Important Standardized Toxicity Testing that Preceded the Black Book

Numerous study designs had been developed prior to publication of the 1949 Black Book.¹ For example, the FDA had already designed and implemented its DDT cancer study and published the study design and findings in 1947.²

In addition, FDA scientists Woodard and Calvery published a list of standard toxicity tests as early as 1943 in the article Acute and Chronic Toxicity-Public Health Aspect.⁷ This document discusses a battery of toxicity studies, and it was intended as a general toxicity study protocol.

In their report, Woodard and Calvery listed the following types of studies that were necessary to conduct “well-controlled toxicological evaluations,” emphasizing the need for testing “new” chemicals or “older substances which have not been properly tested,” stating:

However, with the newer substances, or even with the older substances which have not been properly investigated, it will be necessary to design and carry out well-controlled toxicological investigations, and when the studies are complete, make proper evaluations of the data obtained.

Their procedures were intended to be used to ensure the safety of synthetic materials that were being produced in greater numbers each year, with a special mention of keeping water supplies safe from contamination:

As our population becomes more urban and our consumption of synthetic materials grows with each year, the problem of acute and chronic toxicity becomes increasingly important to the public health. Such concentration of population necessitates handling, transportation, and storage of foodstuffs. This in turn has resulted in the use of preservatives and stabilizers, and in the danger of contamination of foods in manufacturing, refining, and packaging. The exposure of the majority of the population to ever-increasing quantities of synthetic products in foods, drugs, cosmetics, household items, clothing, etc., extends the possibility of chemical sensitizations and poisonings. Urban areas require central water supplies which must be so chosen and maintained that they will not contain harmful impurities. [emphasis added]

They listed the following battery of toxicological tests that were necessary to prove a chemical compound safe for human exposure (Exhibit 2):

Exhibit 2. Excerpt from Woodard and Calvery: Toxicological Tests Needed to Prove a Chemical Is Safe for Human Exposure

- A. Pharmacodynamics
Blood pressure; respiration; heart rate; organ perfusion; isolated tissue preparations; etc.
- B. Acute toxicity
Dosage response curves on three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances.
- C. Subacute toxicity
Large daily doses to one or more species for six to 12 weeks; microscopic pathology.
- D. Chronic toxicity
Three or more species; at least one species for the life of the animal; several dosage levels graduated to produce from no effect up to marked lesions, and possibly shortening life span; microscopic pathology.
- E. External effects
Sensitization; skin irritation; mucous membrane irritation.
- F. Special studies
Reproduction; hematology; absorption and excretion; distribution and storage; effect of diet.

Source: Woodard and Calvery 1943.⁷

It is important to note this battery of toxicology testing protocols was available in the early 1940s and that one of the most important features of the testing protocols was chronic *lifetime* animal testing.

Woodard and Calvery emphasized that, by 1943, laboratory animal breeding programs and animal testing had become standardized to ensure reproducible and consistent laboratory testing results. They also stressed the importance of including control animals:

With the above information, we can now more intelligently plan a chronic experiment. As a matter of fact, if the subacute experiments have been properly started, they may in some cases simply be extended to cover a longer period of time. In any event, the experiment should be conducted on three or more species for the lifetime of at least one of them. Rats, dogs, mice, and monkeys are usually good chronic toxicity subjects. Since the life span of a rat is relatively short-two to three years- and since the rat has been well standardized in many laboratories, this animal is probably the best in every respect for lifetime chronic studies. In such experiments it is well to use several dosage levels of equal gradation from the dose sufficiently high to cause marked lesions, possibly shortening the life span of the animal, to a dose sufficiently low that there are no observable differences between the experimental and control animals. [emphasis added]

Woodard and Calvery also state that multiple species should be used and that several species including “rat, mouse, and guinea pig are well suited for this, since these animals have been quite well standardized.” FDA also stressed that “several dosage levels” be used and the histopathology compared to control animals. They also provide actual examples of FDAs *cancer* studies and emphasized the importance of conducting *long-term* chronic exposures to determine if a chemical compound is carcinogenic:

The value of such long term investigations is well illustrated in the results obtained by Yoshida who fed orthoaminoazotoluene to rats for 200-300 days to produce true experimental liver tumors. It has also been well illustrated in our own laboratory by studies on the glycols. Ethylene glycol, for example, was fed in the diet of rats at levels of 1% and 2%. Kidney and bladder stones appeared in both series of animals. No stones were observed, however, in animals that failed to survive longer than 15 months. Another example is the production of neurofibromas on the ears of rats fed crude ergot. These tumors first appeared

after about 12 months and within 24 months were present on all animals receiving 5% of ergot in the diet. [emphasis added]

Just from this brief discussion, it is clear that the FDA was following a standardized protocol in its cancer testing, which represented the state-of-the-science prior to 1941. The cancer studies were designed to test whether a compound was carcinogenic, and the study design showed they performed well, based on the authors' description.

Woodard and Calvery also note that it is of particular concern to carefully evaluate the toxicity of chemical compounds that bioaccumulate and produce cumulative toxicity because the compounds are stored in the body and are only slowly eliminated:

The absorption, excretion, distribution, and storage of a toxic agent will often guide one in an estimation of its probable effect. If there is an indication of storage of the toxic substance, one should watch for cumulative toxicity. If the material is rapidly eliminated from the animal, and no storage occurs, the toxicity from cumulation likely will not be as serious as the chronic toxicity which may result from the passage of the poison through the system. [emphasis added]

This particular section and warning perfectly describes the types of chemicals (like PCBs and DDT) that should be of particular concern in toxicology testing because both bioaccumulate and are stored in fat tissues in the body for long periods of time.

Woodard and Calvery also importantly stresses that *all* chemicals be tested *before* they enter the “economy of man” to preclude both accidental and intentional exposures:

Extensive investigations carried out on different species of animals are to our minds absolutely essential before a substance should be introduced into the economy of man. The experience and information thus obtained will then enable one to, interpret observations made on human beings whether accidentally or industrially exposed to such a substance, or whether intentionally exposed under carefully controlled clinical conditions. [emphasis added]

This is the first instance I am aware of in which a governmental group of scientists stresses the importance of the precautionary principle, which is based on knowing the toxicity of a chemical

compound *before* it is released into the environment or, as Woodard and Calvery call it, the “economy of man.”

Woodard and Calvery identify many of the critical variables that must be carefully evaluated and controlled when interpreting the results of the battery of toxicology studies they propose (0). These include many of the same variables that Dr. Eaton states are important in standardizing cancer studies, which he claims were only addressed after 1970. These were identified by the FDA in 1943.

Exhibit 3. Excerpt from Woodard and Calvery: Interpretation of Toxicity Data

Interpretation of Toxicity Data

AFTER the toxicological data have been made available, the next major problem which presents itself is the interpretation of these data in terms of their applicability to the public health. The factors involved in making such an interpretation are numerous and complicated. In order that they may be more easily visualized, it seems advisable to present some of them in outline form, followed by a brief general discussion:

- A. Variation between species
 - 1. Response of different species to a single substance.
 - 2. Response of different species to different substances. Contributory factors to the above differences in response are relative surface area and organ capacity, and differences in absorption, metabolism, detoxification, and excretion.
- B. Variation between individuals in the same species
 - 1. Normal distribution and heterogeneity of the population.
 - 2. Physiological condition.
 - (a) Age, sex, weight.
 - (b) External environment.
 - (c) State of physical exertion.
 - (d) Pregnancy and lactation.
 - (e) Presence of food in gastro-intestinal tract.
 - 3. Pathological condition.
 - (a) Renal, cardiac, and hepatic insufficiency, etc.
 - (b) Presence of infectious organisms.
 - (c) Nutritional deficiencies.
 - 4. Multiple exposures.

Source: Woodard and Calvery 1943.⁷

Finally, Woodard and Calvery issue a cautionary note about extrapolating toxicity data derived from animal studies in which only “normal healthy” animals are used directly to humans because that could lead to underestimating the risk a chemical compound could pose to a heterogeneous population of humans that may not all be in great health and whose members may have preexisting medical conditions:

So far, we have discussed reactions on normal individuals. Our experiments have been carried out using normal healthy animals. But in the public which may be exposed, there are many who are most certainly not normal, healthy persons. We must consider then a rather large number of persons who are so unfortunate as to suffer from pathological conditions or disease. The yearly vital statistics are ample proof of the number of people who have cardiac, renal, or hepatic insufficiencies or cancer.

In 1944, FDA scientists also published a similar battery of standardized toxicological tests for new drug applications (van Winkle et al. 1944) in which they cite earlier FDA publications dealing with standardized toxicology tests (Exhibit 4).⁸

These were much more detailed study designs, but as with previous FDA guidance documents, no law required any chemical company to test the chemicals they were producing. Although PCBs were not intended as drugs, these protocols could be used to design a toxicity study for any chemical. Animal studies always precede human studies, so the documents presented the basic framework to those types of tests. Overall, these documents illustrate the sophistication and extent of toxicological testing that had developed by the early 1940s. Many of these tests still form the backbone of FDA's animal toxicology requirements.

Exhibit 4. Excerpt from van Winkle et al.: Objectives of Various Test Categories

(A) *Biochemistry*.—General properties of drug, including solubility, stability; studies of absorption, reabsorption, fate, distribution and excretion of the drug; quantitative data on these points where possible; mode of detoxification (excreted unchanged, oxidized, reduced, acetylated?); effect on enzymes, blood and tissues; chemistry of body fluids and tissues; production of toxic products during course of metabolism.

(B) *Pharmacodynamics*.—Local: Tests of irritation on skin, eye, alimentary canal; intradermal irritation, sensitivity or anesthesia; tests of protoplasmic depression or toxicity, and reversibility of effects on cilia, nerve trunks, mucosa; hemolysis, antihemolysis and blood pigment changes.

Systemic: Action on blood pressure, respiration, muscles, nervous system, cardiac functions, secretions, temperature, voluntary activity, organ perfusion, isolated tissues; effects of vasomotor agents, proteins, fats, metals, solvents and other agents on the actions of the drug; cumulative effects; development of tachyphylaxis; quantitative and qualitative differences in action in different species of animals.

(C) *Experimental Functional Pathology*.—Effects in experimentally induced pathologic states, e. g. smooth muscle spasm, hypodynamic hearts, fibrillations and arrhythmias, hypertension, respiratory depression, edema, shock, burns, anemias.

(D) *Chemotherapeutic*.—Effects in preventing specific experimental infections; effects in combating experimental infections or actions of toxins; antagonists of chemotherapeutic agents, e. g. pus, serum, tissue products; distribution in inflammatory states, e. g. meningitis, dermatitis; minimal effective dosage (ED50).

Source: van Winkle et al. 1944.⁸

3.2. The History of FDA Guidance and Regulations

3.2.1. The FDA Black Book

Dr. Eaton's opinion is based on an incomplete historical review of toxicological and cancer testing in the 1930s through the 1960s. In fact, Dr. Eaton does not mention or cite in his expert report what is perhaps *the* most important milestone in historical toxicology testing: the U.S. FDA Black Book.¹ The FDA was the first governmental agency to document, in detail, standard

protocols for the entire battery of toxicological testing, including long-term cancer studies. These governmental standard protocols were published as: Procedures for the Appraisal of the Toxicity of Chemicals in Foods (Lehman et al. 1949).¹ The authors were among the most highly respected and widely published scientists and toxicologists of the time and had been conducting and publishing studies using the same standard protocols starting in the early 1940s. In this sense, the testing protocols detailed in the FDA Black Book were not a *newly* developed battery of toxicological testing procedures but a compendium of protocols that were being used throughout the 1940s. For example, Drs. Fitzhugh and Nelson began their chronic long-term DDT cancer study in 1943, although it was not published until 1947.²

Dr. Eaton's omission of the Black Book is an indication that his review of historical cancer testing is surficial at best. The Black Book is widely known throughout the field of toxicology and is recognized as presenting the first standardized toxicological testing study designs (I review this important milestone as part of my graduate toxicology course in the introductory lecture). In fact, publication of the Black Book is listed as a key milestone on the FDA web page that chronologically lists the Agency's major accomplishments in U.S. food and drug law:⁹

Milestones in U.S. Food and Drug Law History

1949

FDA publishes guidance to industry for the first time. This guidance, "Procedures for the Appraisal of the Toxicity of Chemicals in Food," came to be known as the "black book."

Dr. Eaton correctly states that Monsanto was under no regulatory obligation to perform any long-term cancer study on PCBs because it was not a drug, food additive, or pesticide used on crops, stating:

It is important to note several points about this excerpt from Dr. Smyth's textbook chapter:

1. This pertains to industrial chemicals not intended for use as pharmaceuticals, food additives, pesticides used on food crops for which other guidelines were developed. PCBs were never marketed and sold for any of these purposes.

2. There is not even a suggestion that two-year bioassays be conducted for the purposes of evaluating potential cancer-causing properties of the materials not used as pharmaceuticals, food additives, or on-crop pesticides

This particular statement is highly misleading and is false by omission. Dr. Eaton fails to mention that there was *no* regulation in 1949 for *any* industrial chemical company to conduct *any* toxicological test—including long-term animal cancer testing—on *any* chemical that was intentionally developed to be a food additive or was an unintentional food contaminant (like DDT or PCB). The only law that existed in 1949 was the FD&C that was passed by Congress in 1938. The FD&C did not require that any chemical be tested. Moreover, FDA’s Black Book *does not* contain any term such as *must* or *shall*. This fact is widely known in the field of toxicology. For example, the introductory textbook I assign to my first-year graduate toxicology students—*Casarett and Doull’s Toxicology: The Basic Science of Poisons* (6th Edition)—states as much.¹⁰ This is the same textbook Dr. Eaton cites as the “widely-acclaimed toxicology textbook.” In Chapter 34, which covers Regulatory Toxicology, Dr. Merrill states:

The oldest of the major health regulation laws, the FD&C Act, was enacted in 1938 and covers food for humans and animals, human and veterinary drugs, medical devices, and cosmetics.

Dr. Merrill notes that the 1938 FD&C law was an amendment of the original Pure Food and Drug Act of 1906, which contained two provisions:

The first forbids the marketing of and food containing any added poisonous or deleterious substance which may render it injurious to health...

The second forbids the marketing of foods containing nonadded [sic] toxicants that make them “ordinarily injurious to health.” [no emphasis added]

He stresses:

Neither of these original provisions required premarket approval; the FDA had the burden of proving that a food was, in the legal vernacular, adulterated.
[emphasis added]

The only amended part of the 1938 FD&C law that provided for regulatory oversight was for truth in advertising *foods* and not *industrial chemicals*. For example, in a detailed discussion of the law, the FDA states:¹⁰

The FD&C Act authorized three kinds of food standards--identity, quality, and fill of container. In 1939, the first food standards were issued for canned tomatoes, tomato purée, and tomato paste. The standards looked like a recipe of listed ingredients. The next standards were for jams and jellies. Junod says, "By 1957, standards had been set for many varieties of foods such as chocolate, flour, cereals, bakery products, milk, cheese, juices, and eggs."

Obviously, if no chemical company was required by any regulation to conduct any toxicity test in 1949 and it was up to FDA to identify food contaminants that could be poisons (only after they were already released into the environment), then the FDA *did not* write the Black Book just for the regulated chemical community. The Black Book was published as a guidance document for *all of the chemical industry*. FDA's very title of the guideline indicates it was not narrowly directed toward a small segment of industry. The Black Book was officially titled, Procedures for the Appraisal of the Toxicity of Chemicals in Foods.¹ As specified by the official title, the Black Book had nothing to do with food additives, which were not regulated for approximately another decade with passage of the FDA's 1958 Delaney Amendment. Therefore, Procedures for the Appraisal of the Toxicity of Chemicals in Foods could apply to Monsanto's PCBs, which were being released in massive amounts into the environment and were later found to contaminate the U.S. food supply.

The FDA intended the Black Book to be used as a guide for chemical industry to test any industrial chemical manufactured in large quantities and to adopt the testing methods detailed within to prevent harmful chemicals from entering the food supply. The Agency specifically noted that it was for "chemicals likely to contaminate foods:"

The body of knowledge accumulated as the result of the above described studies has for its purpose the determination of the relative safety of the chemicals proposed for addition to foods or likely to contaminate foods. [emphasis added]

The introduction to the Black Book was written by Dr. Lehman, who was the Chief of the Division of Pharmacology of the Food and Drug Administration. Dr. Lehman emphasizes two

important points about how critical chronic toxicity testing is for food contaminants compared with toxicological testing for drugs. First, in contrast to drug testing in which exposures are usually limited, human ingestion of food contaminants lasts a lifetime, and U.S. citizens would be “forced” to ingest them daily. Dr. Lehman wrote:¹

As a general rule, drugs are administered for short periods of time so that the duration of the toxicological insult to the body is limited. Even though a medicament may possess undesirable side effects, these usually are outweighed by the therapeutic actions, and the use of the drug can be justified on this basis. On the other hand, when a chemical is added to foods, its ingestion literally is forced upon the individual, and this may continue throughout his lifetime. Under these circumstances, the approach to the appraisal of its safety for use is somewhat different from that for a drug. More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs. [emphasis added]

Dr. Eaton is correct in stating that PCBs were never considered as intentional food additives. However, by 1949, DDT had been released in massive quantities into the environment (not intentionally added to food products), and those releases were known at that time to have resulted in contamination of the U.S. food supply. For this reason, Lehman’s second emphasis in the Black Book introduction appears have been a direct and explicit effort to not only focus on chronic studies to make a determination about chemical toxicity but to change the basic concept and definition of poisons and toxicity that many chemical companies were using to show their chemicals were nontoxic. Lehman singled out chemicals that bioaccumulate and are stored in the body to show they are more toxic than chemicals that are known to be highly toxic based on acute exposures. In this effort, Lehman specifically used DDT as the example chemical compound that was thought to be entirely safe and harmless by the public and scientific communities simply based only on the acute toxicity studies (defined by the LD50) that had been performed. With a simple calculation example comparing a known poison and DDT, the FDA showed this assumption was false and that fat-soluble compounds like DDT are readily absorbed and stored in the body and that chronic exposures increase the body burden to toxic levels even with minute daily intakes (thought to be safe). Lehman provided the following simple example:

More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs. For example, carbolic

acid (phenol) is practically synonymous with the term "poison," and DDT has been considered a quite harmless substance. It has been demonstrated in this laboratory that rats can ingest a diet containing one per cent carbolic acid for a long period of time without producing much harm to the animals. Under similar conditions, rats are injured when the diet contains 0.001 per cent DDT, which indicates that DDT when consumed for long periods of time is at least 1000 times more poisonous than carbolic acid. [emphasis added]

Finally, the Black Book lists all the sequential toxicity tests that are included in any health evaluation, and it presents the same scheme applied today by most academic and industrial toxicologists. At the end of the Black Book, FDA presents an outline of all the standardized tests it discussed in detail in the body of the publication to make it easy for the chemical industry to follow. (See Exhibit 5.)

Exhibit 5. FDA Black Book Outline of Standardized Tests

<p>The salient features of the technics and procedures as presented may be outlined as follows:</p> <ol style="list-style-type: none"> I. Chemistry <ol style="list-style-type: none"> 1. Solubility <ol style="list-style-type: none"> a. Water, oils, and fats b. Physiological fluids 2. Chemical characterization <ol style="list-style-type: none"> a. Composition and constitution b. Stability, purity 3. Quantitative detection in micro amounts II. Acute Toxicity and Pharmacodynamics <ol style="list-style-type: none"> 1. Oral LD₅₀ in several species <ol style="list-style-type: none"> a. Variations between species b. Variations between individuals in same species c. Variations between sexes d. Effect of concentration, age, weight, season, environment, and nutritional state 2. Pharmacodynamics <ol style="list-style-type: none"> a. Intravenous toxicity for determining effect on cardiovascular, respiratory, and gastrointestinal systems, etc. b. Effect on specialized organs and tissues 	<ol style="list-style-type: none"> III. Allergic Response <ol style="list-style-type: none"> 1. Sensitizing reactions in guinea pigs IV. Subacute and Chronic Toxicity <ol style="list-style-type: none"> 1. Subacute toxicity (2 to 4 months' feeding) <ol style="list-style-type: none"> A. Rats <ol style="list-style-type: none"> a. Control b. A low level of feeding about 10 times amount of the chemical as proposed for use in foods c. An intermediate level which may or may not produce an effect on the animal d. The highest level which the animal can tolerate B. Dogs <ol style="list-style-type: none"> a. Control b. Low level at which no effects may be observed. c. Something less than the maximum tolerated level. Effects may be noted d. A near maximum level. Injury can be expected 2. Chronic (long-term) toxicity <ol style="list-style-type: none"> A. Rats <ol style="list-style-type: none"> a. Control b. A level of feeding which will give at least 100 times the concentration in the diet as proposed for food use. c. A level which may or may not produce injury d. The highest tolerated amount which can be fed. Injury can be expected. B. Dogs or monkeys <ol style="list-style-type: none"> a. Control b. A low level which will produce no effects c. A middle level which may or may not produce injury d. A high level approaching the tolerated dose 3. Reproduction studies <ol style="list-style-type: none"> a. Effect of chemical fed continuously through three generations of rats 4. Paired feeding V. Biochemical studies <ol style="list-style-type: none"> 1. Absorption, distribution, and excretion 2. Detoxification mechanism and fate 3. Organ function tests 4. Studies on enzymes VI. Pathology <ol style="list-style-type: none"> 1. Gross examination of organs and tissues 2. Detailed histological examination of organs and tissues of control and experimental animals <p style="text-align: right;">[The End]</p>
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Source: Lehman et al. 1949.¹

3.2.2. Jacobs and Hatfield Historical Reconstruction of Toxicity Testing Standards

My opinion that FDA's Black Book provided detailed procedures and protocols by (at least) 1949 is supported by other scientific experts who have similarly traced the chronological sequence of cancer testing by reviewing the actual scientific publications and regulatory documents to reconstruct cancer testing milestones, as I presented in my expert report. For example, Jacobs and Hatfield (2012) conducted a similar comprehensive review of when industrial cancer testing protocols were standardized and note:¹¹

In the United States, with the passage of the Food and Drug Act of 1906, the Food and Drug Administration (FDA; then known as the Bureau of Chemistry under the US Department of Agriculture) was charged with the responsibility for preventing the adulteration or misbranding of foods and drugs that were marketed to the public. Beginning in 1938, the Federal Food, Drug, and Cosmetic Act gave regulatory powers to the FDA, requiring, among other things, that new drugs be clinically tested and proven safe prior to being sold. The FDA offered guidelines for such studies, but there were no designated standards.

Jacobs and Hatfield support my opinion that, in 1949, the FDA *did* create the first *standardized* guidance document available for the chemical *industry* to follow. Most importantly, they highlight the fact that the Black Book contains a section written by Dr. Fitzhugh that stressed the importance of long-term studies and their design (Fitzhugh published the DDT long-term cancer study with Nelson in 1947):

The FDA first published guidance for industry for assessing the toxicity of chemicals in food in 1949. This guidance was referred to as the "black book" and included a contribution by O. Garth Fitzhugh on the subject of long-term studies and their design. [emphasis added]

Jacobs and Hatfield note that the Black Book states two species (rodent and nonrodent) should be used:

Fitzhugh suggested that for long-term feeding studies, 2 species should be investigated: the albino rat would be studied for a lifetime of about 2 years, and a nonrodent second species (dogs or monkeys) would be studied for at least 1 year.

They also note that the Black Book calls for extensive and comprehensive histopathological examination of all the major organs:

Biochemical and hematology evaluations were to be made at 3-month intervals during the chronic study. At the end of the study, autopsies were to be performed, along with weighing of the principle organs and preservation of tissues for microscopic examination. The pathology evaluation was described in further detail in the black book by Arthur Nelson, indicating that tissues to be evaluated included lung, heart, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary bladder, testis or ovary, prostate or uterus, thyroid, parathyroid, submaxillary salivary gland, 4 levels of brain, hypophysis, bone, bone marrow, and voluntary muscle.

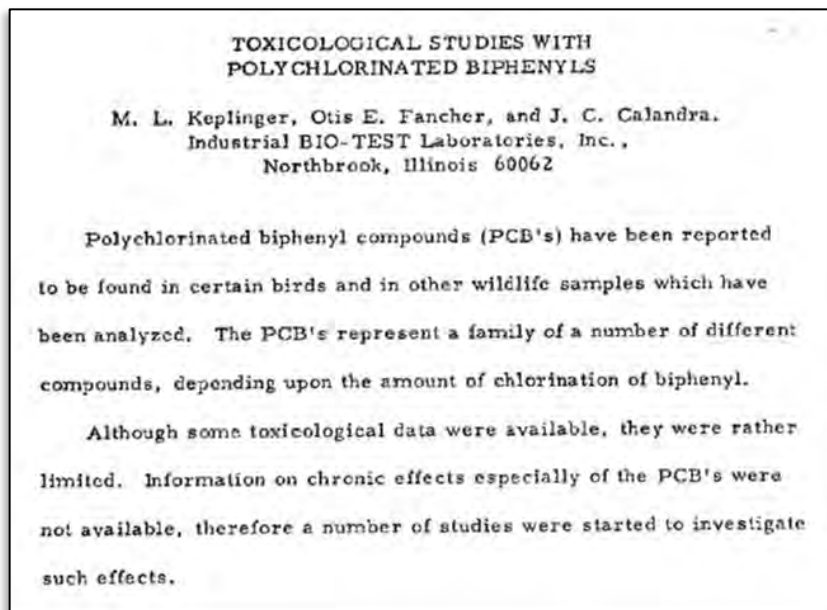
3.3. Monsanto's Lack of Chronic Toxicity Studies

As I discussed in my expert report, Monsanto must have known by 1949 that PCBs, like DDT, were fat soluble (Monsanto manufactured both). However, Monsanto continued to rely on its acute toxicity studies (LD50 studies) as its sole basis for assuming PCBs were not toxic—a conclusion Monsanto communicated to its customers. Dr. Eaton's opinion that Monsanto conducted hundreds of toxicity studies misrepresents the toxicity information that was necessary to correctly evaluate the toxicity of PCBs. Monsanto conducted zero chronic studies to determine the chronic toxicity of PCBs until 1969.

My opinion is that Monsanto should have conducted chronic cancer tests in the 1940s, but certainly after 1949 when the FDA issued guidance to the chemical industry. Monsanto did not perform any toxicity studies, including chronic exposure and cancer studies, until 1969. This fact is supported by Dr. Calandra, who was the president of IBT. IBT was the contract laboratory that conducted the very first chronic study in 1969s as a prelude to cancer studies that were initiated in 1969. Dr. Calandra states the reason for starting those chronic studies was that no chronic toxicity study had been conducted for PCB. In a Monsanto memo (TOXSTUDIES0996), Drs. Keplinger, Francher, and Calandra stated (Exhibit 6):¹²

Information on chronic effects especially the PCBs were not available therefore a number of studies were started to investigate such effects. [emphasis added]

Exhibit 6. Excerpt from IBT Memo From Keplinger, Fancher, Calandra



Source: IBT, Toxicological Studies with Polychlorinated Biphenyls (Bates 0531555; TOXSTUDIES0996)

It should be noted that in reviewing what Monsanto is defining as “toxicity” tests conducted from 1929 through the mid-1960s (before they conducted their first chronic testing) and comparing them with the FDA Black Book list were not toxicity tests. The only tests Monsanto conducted for PCBs were LD50 studies to determine the amount of PCBs that were lethal in the rat (and only on rats, rather than on the several species necessary and stated in the 1949 Black Book—so even the LD50 studies were not conducted according to the standard). Monsanto also conducted brief allergic sensitization studies and very short irritant studies on the skin and eye to evaluate worker exposures.

3.4. Dr. Eaton: Table 12 (Dr. Eaton Report, page 74)

3.4.1. Pre- and Post-1970 Designations

I have carefully reviewed Dr. Eaton’s Table 12. In the first column, he lists what he calls the “Study Design Parameters.” He then lists what he believes the state-of-the-science was for each

of those parameters in the “Pre-1970” (column 2) period, which he juxtaposed next to the “Post-1970” (column 3) corresponding criteria. It is not clear why he arbitrarily chose 1970 to divide the two periods. As I stated previously, standardized protocols are (with few exceptions) developed to meet the requirements of a new *government* law or regulation or by a governmental scientific body like the Centers for Disease Control and Prevention (CDC) or the National Toxicology Program (NTP). I am not aware of any new regulatory laws, requirements, or standardized protocols developed in 1970. There were certainly no new U.S. Environmental Protection Agency (EPA) laws or regulations because the Agency was not created until 1970. FDA’s standard procedures were developed in 1949—although they have continuously been further refined over the decades.

I assume that Dr. Eaton believes the 1970 date is important only because that is when Monsanto finally started its chronic toxicity studies, including cancer studies. Dr. Eaton appears to be attempting to show that Monsanto somehow could not have conducted long-term cancer studies *before* 1970 because there were no standards.

3.4.2. Dr. Eaton Table 12 vs. FDA Black Book Guidelines

I carefully reviewed Dr. Eaton’s summary table for each of the Study Criteria Parameters listed in the Pre-1970 Practices column and compared those to what was detailed in the 1949 FDA Black Book guidelines. Obviously, 1949 was well before 1970, so I focused on the Black Book to determine whether Dr. Eaton was correct and when standardized protocols were first available for Monsanto or any other industrial chemical company to use in order to test their chemical products in a consistent and effective manner. To show that the FDA had developed standard practices available for industry as early as 1949, I have added a fourth column to Dr. Eaton’s table (designated as *Dr. DeGrandchamp*). Furthermore, in order to preclude any bias from my review and interpretation of the Black Book, I have inserted the specific information quoted from that publication. With this approach, I was able to evaluate Dr. Eaton’s summary opinion for his pre-1970 analysis, as well as whether the criteria he listed as being available only post-1970 were actually available in 1949. (See Exhibit 7)

Exhibit 7. Dr. DeGrandchamp Modification of Dr. Eaton Table 12: Animal Cancer Testing Study Design Practices

(Pre-1970 and post-1970: Dr. Eaton; 1949: Dr. DeGrandchamp)

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949</i>¹
Number of Dose Groups	Typically a single dose group	Minimum of three or more groups	RAT: MINIMUM 3 DOSE GROUPS NON-RODENT DOG OR MONKEY: MINIMUM 3 DOSE GROUPS "Dosage levels are kept adjusted to the body weight changes."
Method of Administration (e.g., Dermal, Inhalation, Gavage, Dietary)	Dermal or inhalation exposure (assess occupational exposure)	Dietary or gavage to ensure dose	INGESTION: FOOD CONTAMINANTS ARE EATEN FOR A LIFETIME "The substance may be administered by stomach tube [gavage], capsules, or by mixing with the animals' food."
Length of Administration (How Long)	Variable	Established period of time: Lifetime ~ 2 yrs	ESTABLISHED PERIOD OF TIME: LIFE SPAN IN RAT ~2 YRS - RATS SACRIFICED AT 2 YEARS. FOOD CONTAMINANTS MUST UNDERGO LIFETIME CHRONIC TOXICITY TESTING: "On the other hand, when a chemical is added to foods, <u>its ingestion literally is forced upon the individual, and this may continue throughout his lifetime.</u> " "More emphasis must be placed <u>on the development of chronic effects</u> rather than on acute and subacute effects as is the case with drugs."
Animal Care	Not standardized	Rigidly controlled, standardized animal medicine practices	RIGIDLY CONTROLLED: "Rats are housed individually in an air conditioned laboratory and records kept of all observations for the duration of the experiment."
Tissue analysis	No uniform classification system	Established classifications	EXTENSIVE FDA DISCUSSION OF PATHOLOGICAL HALLMARKS OF CANCER DESCRIBED EARLIER—1947 (Fitzhugh and Nelson 1947)
Pathology review	Single pathologist	Multiple pathologists	COMPREHENSIVE PATHOLOGICAL EXAMINATION OF TREATED AND CONTROL ANIMALS: "No matter what amount of pathological study is done, at least a little and sometimes much of its value is lost if it is not done with

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949¹</i>
			<p><i>good control material, and against a background of experience</i>"[no emphasis added]</p> <p>ALL PATHOLOGICAL EXAMINATIONS SHOULD BE BLIND WITH PATHOLOGIST IGNORANT OF TREATED AND CONTROL TISSUES: "An excellent stimulus to objectivity in examination is for the pathologist not to know, until a preliminary report has been made, which are control and which are treated animals.</p> <p>"1. Gross examination 2. Thorough microscopic morphological histopathological pathology and histology required 3. Pathological examination "should be detailed enough to show the lowest dosage level of the chemical capable of producing it in even the slightest degree." 4. At minimum "detailed microscopic (and, of course, gross) examination of enough animals to give statistical significance to the results. 5. Pathological examination of organs: lung, heart, liver, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary bladder, testis (or ovary), prostate (or uterus), thyroid, parathyroid, submaxillary salivary gland, four levels of brain, hypophysis, bone, bone marrow, and voluntary muscle. 6. Histopathology: routine stains, special stains for identification of pigments, fat stains on frozen sections, stains for glycogen, and imprints or smears of bone marrow.</p> <p>"By detailed study is meant autopsy and gross examination of all experimental and control animals, except perhaps those in which the experimental period has been only a day or two, and microscopic examination of all major organs and tissues in sufficient numbers to make reasonably certain whether the chemical is or is not causing injury or change in any of them. If there is any effect, then the examination should be detailed enough to show the lowest dosage level of the chemical capable of producing it in even the slightest degree."</p> <p>ORGANS TO BE EXAMINED: "A list of organs routinely examined in our dogs may be of some help as a guide. These include lung, heart, liver, spleen, pancreas, gall bladder, lymph nodes, stomach, small intestine, colon, kidney, adrenal, urinary</p>

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949</i> ¹
			<p>bladder, testis (or ovary), prostate (or uterus), thyroid, parathyroid, submaxillary salivary gland, four levels of brain, hypophysis, bone, bone marrow, and voluntary muscle.”</p> <p>REASON HISTOPATHOLOGY REQUIRED “The most legitimate objection that may be made to the inclusion of microscopic pathological study in a chronic toxicity experiment is that if growth, mortality, and reproduction are unaffected, and if gross examination at autopsy shows no difference from the controls, then microscopic examination would according to the objector) in all probability show no difference. There are several reasons why it should be done nevertheless.” THREE REASONS ARE STATED.</p> <p>“Generally speaking, slight but significant microanatomical effects frequently will be found at a dosage level where mortality and weight are unaffected.”</p>
Statistical practices	None or non-standardized	Highly standardized	PATHOLOGICAL LESIONS IN DOSED AND CONTROL GROUPS ARE STATISTICALLY ANALYZED, DOCUMENTED AND STATISTICAL SIGNIFICANCE CALCULATED
Group Size	Variable	Larger numbers of animals, animals individually tracked and assessed	<p>RAT: 80 RATS PER STUDY “In the rat experiment, at least four groups of animals, each consisting of a minimum of ten males and ten females, are employed and distributed as follows: (a) a control group, (b) a group on a diet containing 100 times as much of the ingredient as is proposed for use in food, (c) a group fed a diet containing the highest tolerated amount of the substance, and (d) a group given an intermediate dosage level.”</p> <p>NON-RODENT: 24 DOGS/MONKEYS PER STUDY A minimum of 3 male and 3 females in each of 3 dose groups and a control group “Three animals each on four dosage levels. These are assigned” to (a) a control group, (b) a group on a low level which will produce no damage, (c) a group on a high level which approaches the tolerated amount, and (d) a group on a middle level which may or may not produce injury.</p>

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949¹</i>
Species	Multiple species	Rats or mice, consistent strain or sensitive strain	RATS HAVE BEEN STANDARDIZED: “The albino rat has been a <u>standardized</u> animal and has a life span of about two years, it is the most convenient test object for long-term feeding experiments” NONRODENT SPECIES: DOG Or MONKEY Nonrodent species required.
Gender	Random gender selection	Both genders or most sensitive gender	BOTH GENDERS ARE DOSED
Age	Varied	Studies begin at specific, young ages	DOSING IS STARTED IN YOUNG WEANLING RATS
Historical Controls (Summary of Control Animals)	Generally not available	An integral part of study design	CONTROLS ARE ALWAYS USED FOR SPONTANEOUS TUMOR INCIDENCE IN EACH STUDY “Tissue alterations resulting from the administration of- drugs or chemicals are frequently not of a new or special type; rather, there is often but an increase in the incidence or degree of some type of abnormality already present in that particular laboratory strain of animal. [original emphasis] “The above is but another way of saying that enough animals must be examined to give the observations <u>statistical significance</u> , and that the common "spontaneous" lesions absolutely cannot be disregarded.” “For example, older rats on control diets may show a relatively slight degree or incidence of a chronic nephritis or nephrosis. Their mates fed a certain chemical may show the same histological changes in the kidney, but the process, on the average, will be of greater intensity or frequency.” [emphasis added] “Control animals in experiments involving repeated subcutaneous .injections, stomach tubing, and so on, should not be simply untreated animals, but should be given injections and tubings as similar as possible to the test group, except of course for the presence of the chemical to be tested.”
Doses Administered (Total Dose and Variability Within Study Period)	May have relied on a minimum range finding study (dose could be adjusted during study)	Use of a subchronic study to set chronic dose levels (doses aren't typically adjusted)	SUBACUTE/SUBCHRONIC STUDIES MUST PRECEDE CHRONIC STUDY TO SET CHRONIC DOSING LEVELS

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949</i> ¹
			<p>"The two series of animals are fed their respective diets for a period of <u>two to four months.</u>"</p> <p>"The first consideration for a chronic study is a "pilot" experiment designed to serve as a guide in planning a long-term experiment. Beginning with weanling rats, several dosage levels are administered for periods of two to four months, thus covering the period of rapid growth. Four groups of weanling rats of the same sex are probably the minimum which can meet the requirements."</p>
Observations	Limited	Comprehensive	<p>COMPREHENSIVE</p> <p>"Observations should be made on the rate of growth, food and water intake, fertility, Mortality, general appearance, and behavior of the experimental animals. Blood and Biochemical studies should be made during the experimental period. Upon completion of the feeding period, all animals should be autopsied for gross changes in the organs, the principal organs should be weighed, and tissues preserved for histopathological study. Animals showing significant loss in weight, the development of a tumor, or other evidences of severe abnormality during the experimental period should be sacrificed and the tissues preserved for histopathological study. Tissues of animals dying within the experimental period also should be preserved for study. With these facts in mind, a general plan which is designed to throw light on this question is given below."</p> <p>MANY ADDITIONAL DETAILS PROVIDED [emphasis added]</p>
Intervals of Administration (On/Off)	Variable intervals	Continuous	<p>NO ON/OFF DOSING NECESSARY: HUMANS ARE FORCED TO EAT FOOD CONTAMINANTS ENTIRE LIFETIME</p>
Test Substance	Purity impossible to determine	Purity confirmed, contaminants identified	<p>SOLUBILITY IN FATS AND OILS MUST BE DETERMINED AS WELL AS IMPURITIES:</p> <p>"The most important single physical characteristic of a compound is its solubility, not only in aqueous media, the common basis of physiological fluids, but also in fats and oils. <u>So much hinges on this property of solubility that it frequently spells the success or failure of an otherwise promising compound.</u>"</p> <p>"The seriousness of this lack can be brought into even sharper relief when we consider how necessary a good quantitative method is to the proper evaluation of a compound: (1) Determination of solubility by simple</p>

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949</i> ¹
			<p>physical means alone is frequently impracticable.</p> <p>(2) No control operation in a manufacturing plant is reasonably secure from error without an adequate chemical method which ensures that its product be of uniform composition, <u>free from impurity</u>, and the amount of the compound in question held within precise limits.</p> <p>(3) It is impossible to assemble information on the biochemical behavior of a compound, discussion of which will be considered in another section."</p> <p>CHEMICAL PROPERTIES MUST BE DETERMINED: "This point of view is based chiefly on the fact that it is the correlation of chemical, physical, biochemical, and toxicological knowledge about a compound which is necessary in order to evaluate its safety properly."</p>
Source of Test Compound	Not specified	Well documented	SOURCE OF TEST COMPOUND DETERMINED BY CHEMICAL MANUFACTURE
Record Keeping	No requirements	Good Laboratory Practice (GLP) regulations	<p>"Records kept of all observations for the duration of the experiment. A larger number of rats per group [than the minimum stated] and more dosage levels of the substance under study will aid in the interpretation of results."</p> <p>GLP REGULATIONS WERE NOT DEVELOPED UNTIL 1978 GLP was only created following the U.S. EPA/FDA audit of <u>Industrial BIO-TEST Laboratories (IBT)</u> studies in which several hundred studies contained deliberate fraudulent data and information.</p>
Additional Analysis (e.g., Hematology, Urinalysis)	Limited	Comprehensive analyses	<p>COMPREHENSIVE ANALYSIS:</p> <ol style="list-style-type: none"> 1. Determine: absorption, excretion, storage, detoxification mechanisms, 2. Hematology 2. Urinalysis 3. Molecular Mechanism: "Depending upon the individual case, these experiments may involve studies on isolated tissues or organs, careful pharmacodynamics, electrocardiograms, electroencephalograms, chemical antidotes, chemical studies of blood pigments, isolated loop or pouch studies, renal clearance, etc." determination are made at intervals of about three months on representative animals in each group."

Dr. Eaton STUDY DESIGN PARAMETERS	Dr. Eaton PRE-1970 PRACTICES	Dr. Eaton POST-1970 PRACTICES	Dr. DeGrandchamp PRE-1970 PRACTICES (1949) BASED ON FDA'S BLACK BOOK STANDARDS <i>Lehman et al. 1949¹</i>
			<p>IDENTIFY CHEMICAL THAT BIOACCUMULATE OR ARE STORED IN THE BODY</p> <p>“Consider compounds E and F of essentially equal acute toxicity but on subacute oral exposure lasting three weeks, compound E shows greater toxicity. Examination of the tissues of the animals shows <u>marked storage</u> of compound E. with little or none of compound F. <u>Here storage in the tissues can be regarded as a potential hazard</u>, and explains the increase in subacute toxicity of compound E over F. Compound E would therefore be <u>excluded from consideration</u>.” [emphasis added]</p>
Laboratory Design	Not standardized	Clean/dirty corridor systems and Standard Operating Procedures	<p>STANDARD OPERATING PROCEDURES USED</p> <p>“Rats are housed <u>individually</u> in an air conditioned laboratory and records kept of all observations for the duration of the experiment.” [emphasis added]</p>
Study Segregation	Not standardized	One study per room	SEE ABOVE

3.5. Pre-1970 Cancer Study Design Practices

It is important to note that all of Dr. Eaton statements about which standards were developed pre-1970 lack veracity. Moreover, Dr. Eaton's pre-1970 statements are gross oversimplifications regarding *standardization practices* and suggest that cancer studies during that time were simply scattershot. In fact, academic and industrial toxicologists pre-1970 would *never* have simply reviewed voluminous published studies cancer studies and somehow formulated a cancer testing protocol by amalgamating all the cancer studies and distilling them into a study design to test a chemical for carcinogenicity. Nor would they just randomly select a published study and follow the experimental design. That is not how any scientist would proceed during the pre-1970 period, nor would it be true today. Scientists review extensive published studies and typically select the best and most robust study design to follow.

Dr. Eaton suggests that Monsanto could not have conducted any cancer study pre-1970 because not all study designs were *identical*. This defies not only the standard generally accepted practice a toxicologist would follow to find the best verified study protocol with which to conduct a cancer study for an industrial chemical, it also defies logic. Cancer studies were expensive and time consuming, and labor-intensive. They lasted 2 years, so no toxicologist would even consider starting a cancer study before extensively reviewing the published literature to design the most cost-effective and scientifically tenable testing protocol. Dr. Eaton's opinion is simply wrong because he creates a false choice between conducting a cancer study using a *bad study design* or refusing to conduct any study (the option Monsanto chose).

Had Monsanto investigated performing a cancer study on PCBs in the 1940s, it would have only needed to find *one* robust study with a solid, well-described protocol and preferably one that was *relevant* to an industrial chemical. I have discussed many such studies in this rebuttal report and in my original expert report, but one prime example of a solid study in the 1940s was the 1947 Fitzhugh and Nelson FDA DDT cancer study.² This study was an FDA-published study.

I have reviewed the 1947 FDA study; it is a robust analysis showing that DDT was a carcinogen and control animals were used to assess spontaneous tumors. All Monsanto needed to do was adopt the FDA study design and implement it; Monsanto would then have found that its Aroclors were carcinogenic—just like the FDA found DDT to be carcinogenic.

3.5.1. GLP Practices Were Not Established Until 1978

Dr. Eaton correctly states that *Good Laboratory Practices* (GLP) programs were not developed before 1970. However, it is not clear that he realizes why this particular fact is so important to this case. He notes that GLPs were not established before 1970, but he fails to appreciate that the *primary reason* they were first established is because of the fraudulent and false studies IBT submitted to the government. Moreover, the relevance of this fact is that IBT was also the *sole* laboratory Monsanto used to conduct all of its PCB cancer studies in the early 1970s; those tests were also shown to be deliberately fraudulent, containing much false information and data, and were submitted to U.S. EPA.

The U.S. EPA and FDA were forced to standardize and codify GLPs in 1978. As I mentioned above, the only notable difference between the post-1970 standard practices and those I listed above directly from the 1949 FDA Black Book is that there were no GLP procedures when the Black Book was published. There is no indication from the hundreds of historical publications I have reviewed that there was any concern in the 1930s through the 1960s about dishonest scientists or testing laboratories conducting fraudulent studies and producing false documents that purported to show a chemical was safe when it was not (although there were likely scientists who did). This perception changed after the U.S. EPA-FDA audited the laboratories and records from the IBT laboratories. IBT conducted hundreds of toxicity studies for the chemical industry, and hundreds were found to be *deliberately* fraudulent studies based on *intentionally* included false data and information about their test results. These fraudulent IBT studies were submitted to the government, which resulted in many untested and potentially toxic chemicals being used as pesticides; this could have posed significant health risks to the U.S. food supply and the general population because their toxicity was unknown.

In 1983, the U.S. EPA provided a summary of its review of IBT's blatant disregard of generally accepted laboratory practices that all other laboratories followed and the fraudulent reports submitted by IBT to the government.¹³ The scandal shook the chemical industry and governmental agencies:

The IBT scandal shook the industry and governmental regulators. Obviously, steps had to be taken, not just to deal with the IBT situation itself, but to ensure

that data providing the foundation of regulatory decisions in the future are adequately prepared and scrutinized. Thus, another result of the IBT case was the establishment in 1977 of a joint EPA-FDA audit program to help ensure that another IBT situation has not occurred and will not in the future. [emphasis added]

Dr. Seaton from the FDA provides some details on the IBT debacle and what U.S. EPA and the FDA found during their audit in a 2017 presentation to the Society of Toxicology (Dr. Eaton and I are both members) titled, *An Update on FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies Proposed Rule*.¹⁴ The details Seaton provides on the history of GLPs and IBT's role and standard operating practices in triggering the GLP supports my opinion and shows Dr. Eaton is incorrect for the following reasons:

1. GLPs were first developed in 1978 (not 1970) because of IBT's fraudulent studies;
2. GLPs were developed in 1978, well after Monsanto already began conducting cancer studies;
3. The inspection of IBT's laboratories revealed animal toxicity testing conditions were appallingly dirty, with standing water on the floor. This disproves Dr. Eaton's opinion that after 1970, cancer studies were conducted under clean and carefully controlled conditions in which toxicology testing laboratories kept meticulous and reproducible testing records. This is at least not true in the case of the IBT studies.

Dr. Eaton's Table 12 seems to suggest that by arbitrarily selecting the 1970 time point, Monsanto's IBT PCB cancer studies were conducted under the GLP protocols, when this would have been impossible because GLP were not established until well after Monsanto submitted its IBT reports to the government.

In 2014, the U.S. Government Accountability Office issued a report to Congress (*Pesticide Safety: Improvements Needed in EPA's Good Laboratory Practices Inspection Program*) on the current status of the GLP to evaluate any improvements in the laboratory inspection process.¹⁵ This report presents a short summary of the history of the GLP program, focusing on why formal GLPs were developed in the first place. The GAO notes that U.S. EPA and FDA have each developed their own GLP standards. It was necessary to develop these GLPs to address a very

distressing period in the field of toxicology that is well-known to most toxicologists and involved the submission of false and fraudulent reports by IBT. This was the laboratory that conducted the 1971 series of Monsanto PCB studies and submitted those reports to U.S. EPA and other scientists. IBT was responsible for all long-term cancer testing studies conducted on PCBs for Monsanto. As a result of the EPA and FDA investigations of IBT, several hundred studies were invalidated.¹⁵

EPA and FDA have each developed their own GLP standards to address problems found with laboratory studies submitted for the agencies' review. Investigations by these agencies in the mid-1970s revealed that some studies had not been conducted in accordance with commonly accepted laboratory practices... In 1983, EPA published its GLP standards for pesticide toxicology studies, and in 1989, EPA extended the standards' coverage to include nearly all research data supporting pesticide registrations under FIFRA.

The U.S. EPA and FDA established these GLP procedures only after discovering the *deliberate* fraud in IBT testing procedures and false reports:¹⁵

EPA and FDA have each developed their own GLP standards to address problems found with laboratory studies submitted for the agencies' review. Investigations by these agencies in the mid-1970s revealed that some studies had not been conducted in accordance with commonly accepted laboratory practices. For example, according to an industry representative, one of the first laboratories to attract regulatory and media attention was Industrial Bio-Test Laboratories (IBT), a contract toxicological research laboratory that conducted much of the U.S. toxicological testing at the time. As a result of EPA's and FDA's investigations of IBT, several hundred studies were invalidated because of deliberate fraud, and hundreds of chemicals had to be retested. Specific findings included poor recordkeeping, testing conducted by untrained and unqualified personnel, and data fabrication. For example, data were submitted on rats that had previously been reported as deceased. [emphasis added]

Accordingly, Dr. Eaton may be correct in stating that some laboratories followed *common laboratory practices*, but they did not follow GLP procedures until after they were codified in 1978.¹⁴ More importantly, IBT, *in particular*, did not follow either GLP or common laboratory practices particularly with regard to the PCB cancer testing.

In his presentation to Dr. Seaton reconstructs the history that led to the GLP being developed and IBT's role in the following summary:

Industrial BIO-TEST Laboratories (IBT)

- *1975, FDA received a tip that there were problems with tests submitted to FDA.*
- *The medical officer found study data was 'unbelievably clean', no rats on 2-year study developed cancer.*
- *The medical officer found enough deficiencies to warrant an inspection.*
- *Visit to IBT in April 1976: "What we found there is enough to make your hair stand up." [emphasis added]*

IBT did not collect terminal blood and urine samples, which Dr. Eaton states was standard practice, but neither did they keep reliable testing records, which he states was also *standard practice* post-1970.¹⁴

"Magic Pencil Study"

- *Terminal blood and urine samples were not collected.*
- *Draft data tables for the blood and urine assessments were blank, as expected.*
- *However, the final report not only had values reported, but had the technical writer's name written in. All of those results had been fabricated. [emphasis added]*

Although Dr. Eaton indicates that post-1970 studies were conducted under carefully controlled laboratory conditions, IBT's studies were conducted under such dirty and appalling conditions with such little concern for the well-being of the laboratory animals' health that the animals actually suffered and died. These practices invalidate the IBT studies. Furthermore, as a toxicologist who has conducted many toxicity studies and cared for laboratory animals, I can

state that IBT's animal care borders on unnecessary animal abuse. Dr. Seaton describes the following:

"The Swamp"

- *System designed for automatic watering and flushing waste from cages rarely worked properly.*
- *Faulty nozzles sprayed the room with a continuing mist. The floor was at times submerged under 4 inches of water.*
- *Technicians only entered the room wearing rubber boots.*
- *Clogged water nozzles and drain hoses drenched some rats in a cold spray, while others died of thirst. [emphasis added]*

As a result of the above horrific descriptions of IBT's testing procedures and deceptive record keeping, 71% of the IBT studies were deemed invalid:

Regulatory Action

- *FDA and EPA reviewed compounds that relied on IBT for data in support of safety.*
- *Called into question the reviews of more than 200 pesticides, many were retested at manufacturer's expense.*
- *618 of 867 (71%) of studies audited by the FDA were invalidated for having "numerous discrepancies between the study conduct and data". [emphasis added]*

This indicates that by relying on the false IBT pesticide studies, U.S. EPA unknowingly approved more than 200 pesticides that were used on food products and had never been tested for toxicity.

In addition to the above discussion of IBT's role in prompting regulatory agencies to develop the GLP, I have also reviewed the transcript of the 1991 PCB trial (WATER_PCB-00056547) in

which IBT laboratory assistant toxicologist Mr. Philip Smith testified that some of the above statements were true and correct as they relate to IBT's Monsanto PCB studies of Aroclor 1260, 1254, and 1242 in the early 1970s.¹⁶ Smith personally worked on these studies at the direction of Dr. Paul Wright, the section head of toxicology who was later indicted and convicted of crimes relating to IBT's fraudulent testing activities. Smith's testimony also shows Dr. Eaton's opinions regarding post-1970 standard practices are incorrect at least with respect to Monsanto's IBT PCB cancer testing studies. For example:

1. Dr. Eaton stated that animal observations during the studies were comprehensive. Mr. Smith invalidates Dr. Eaton's opinion because Mr. Smith testified that many of the animals were not even weighed during the study. Furthermore, at the end of the study, he was instructed by Dr. Wright to simply make up animal weights based on historical weight data from other studies. Animal weights are a sensitive and critical indicator of an animal's overall health. Weighing animals during a chronic cancer study is routine, and this metric is carefully monitored during the entire study period. These measurements are so critical to chronic studies that a 10% decrease in body weight is conventionally considered *a toxic effect by itself*. Body weight is also critical in dosing, because dosing is *fundamentally based* on body weight. Simply put, without the body weight, the amount administered to an animal cannot be calculated.
2. Dr. Eaton stated that GLPs were followed post-1970 with regard to the overall design of the study.

Mr. Smith notes that this was not true for the IBT–Monsanto studies. IBT followed egregious testing protocols that included, most importantly, not noting that PCB-treated animals died at a high rate. Mr. Smith notes that the survivability was very poor, stating, “*There were very few animals that survived the length of the study.*” In addition to the obvious fact that animals died at a high rate (and this information was falsified in IBT's records), Mr. Smith's statement is diametrically opposite from what Dr. Eaton stated with regard to the number of animals necessary to conduct a standard cancer study. First, Dr. Eaton stated that large numbers of animals are necessary for cancer studies. While IBT may have *started* with a large number of animals (which it did not, as I discuss below), IBT did not have many animals that survived the length of the study. Second, Dr. Eaton stated that statistical analysis was *highly standardized*,

which is a false statement on the face of the facts. Highly standardized analyses require a large number of animals, but are completely worthless if most animals die and cannot be examined.

1. Dr. Eaton also stated that good recordkeeping was standard practice post-1970, but neither the animal weights (as discussed above) nor animal deaths were recorded by IBT in their post-1970 studies.
2. Dr. Eaton also states that GLP post-1970 studies carefully observed animals, and a comprehensive histopathological evaluation of their organs was conducted.

Mr. Smith's testimony refutes this for the IBT PCB cancer studies. He notes that not only comprehensive pathological evaluations were not conducted on some animals but that it was not possible to do so. He testified that when animals died during the study:

That there were many animals that were so badly decomposed that they were worthless for pathological examination...I would say 60 percent of the animals either had—were too badly decomposed or there was no record of them leaving the studies. They just disappeared.

Finally, according to Mr. Smith's testimony, the deviations from GLP listed above for the IBT studies were neither unique nor isolated. In response to a direct examination question of whether Mr. Smith regarded the Monsanto IBT PCB studies as *shameful or irregular*, Mr. Smith responded:

At the time that study was done, no. It was pretty well standard operating procedure for everything.

3.5.2. Dr. Eaton Relies on IBT False Reports

For all the reasons presented in the above section, I believe that any of Dr. Eaton's statements or opinions directly or indirectly based on any IBT–Monsanto memo, document, conclusions, or toxicological testing reports should be considered scientifically untenable and disregarded. In 1981, Monsanto (MONS213337; Further discussed in section 3.6.3) also came to the same conclusion that the IBT studies did not follow a testing protocol and was an invalid study.¹⁷

Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a, b, c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals. Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers. [emphasis added]

The following numerous sections summarize some of the citations, statements, and opinions in Dr. Eaton's report where he cites or relies on Monsanto's IBT studies. Since the IBT studies were fraudulent, any opinion based on these studies should be considered *not scientifically tenable and should be disregarded*.

3.5.2.1. *Dr. Eaton Presents the IBT Studies as Not Showing Cancer (Page 40)*

The following is Table 4 from Dr. Eaton's Report (0).

Exhibit 8. Table 4 from Dr. Eaton Report: Summary of 2-Year Carcinogenicity Bioassays Completed on Commercial Mixtures of PCBs, 1971

Table 4. Summary of 2-year carcinogenicity bioassays completed on commercial mixtures of PCBs

Year	Species and strain	Test group numbers	Dose groups (ppm)	PCBs studied	Positive for cancer (M, F)*	Reference
1971	CR Albino rats; males and females	8 groups; 50 per group	0, 1, 10, 100	Aroclor 1242	No, No	(IBT, 1971a)
				Aroclor 1254	No, No	(IBT, 1971b)
				Aroclor 1260	No, No	(IBT, 1971c)

Source: Eaton 2019.⁴

3.5.2.2. *Dr. Eaton Compares IBT Studies to Historical Cancer Studies (Page 41)*

The IBT studies were fraudulent and this statement makes a comparison to those studies:

It is important to note, however, that the 'positive' Brunner/Mayes study utilized a formulation of Aroclor 1254 that was manufactured by a different process than had been used prior to 1974 and had considerably higher amounts of DL-PCBs, compared to 'older' Aroclor 1254 formulations used in the NCI 1977 study and the 1971 IBT study (Kodavanti et al., 2001). The DL-PCB 'TEQ' value for the Aroclor 1254 lot used in the Brunner/ Mayes study was 11 times higher than the TEQ value of Aroclor 1254 that was used in the largely 'negative' NCI 1978 and IBT 1971 studies (Kodavanti, et al., 2001).

3.5.2.3. *Dr. Eaton States that Monsanto Had No Reason to Conduct Any Cancer Test; Nevertheless, It Contracted with IBT to Conduct the First (Fraudulent) 2-Year Cancer Study (Page 92)*

It is not clear why Dr. Eaton is stating that 2-year cancer bioassays have 'seldom been done' because the 1949 FDA Black Book states this is a standard protocol. Dr. Eaton goes on to state that IBT did not detect carcinogenic activity in their cancer studies, which is not correct. IBT did detect carcinogenic activity despite presenting false data in their reports.

Testing requirements could conceivably include a requirement for a 2-year cancer bioassay, although this has seldom been done. Thus, given the absence of any of the triggers noted above, and the complete absence of any indication from workplace monitoring that PCBs had increased cancer risk among workers, Monsanto had no reason to conduct a 2-year carcinogenesis bioassay. In fact, they were not under any obligation to do so when they contracted with IBT in the late 1960's to conduct the first ever 2-year rodent carcinogenicity study with Aroclors, which did not demonstrate carcinogenic activity in that study.

3.5.2.4. *Dr. Eaton Presents a Lengthy Discussion of the "Negative" Findings of the IBT Report (Page 174)*

Dr. Eaton presents a lengthy discussion of the "negative" cancer results from the IBT study that should be discredited from his opinions.

- IBT (1971b) – Monsanto contract study on Aroclor 1254

- Table A3- 1. Histopathology of the liver of rats treated with Aroclor 1254

3.5.2.5. Dr. Eaton Assesses “Time to Tumor” Discussion (Page 183)

It is not clear why Dr. Eaton would rely on “time to tumor” (which is more routinely called latency period) when Dr. Eaton states there were no tumors.

3. Summary of ‘Time to Tumor’ information in these studies:

IBT Studies – no useful ‘time to tumor’ data were provided in these studies. But there were also no tumors found, even at the end of the study, so these are largely non-informative as to when liver tumors might first appear.

3.5.2.6. Dr. Eaton Summarizes IBT False Tumor Incidence Rate (Page 186)

In Exhibit 9, Dr. Eaton has relied on IBT incidence rates as his evidence that there were many studies published that did not show Aroclors were carcinogenic. Dr. Eaton’s conclusions should therefore not be considered scientifically defensible. In addition the table appears to be incomplete or wrong. Monsanto’s Memo (MONS043459) state that the early Kimbrough incident rate of “neoplastic nodules” and “hepatocellular carcinomas” was 170/180 animals not 26/184 as presented in Dr. Eaton’s table. The entire table and any conclusions from the table should be discredited.

Exhibit 9. Table A3–5 from Dr. Eaton Report: Summary of Tumor Incidence from 2-Year Rat Bioassays on Various Aroclors at 100 ppm

Table A3- 5. Summary of tumor incidence from 2 year rat bioassays on various Aroclors at 100 ppm

100 ppm Aroclor 2 yr studies – Excess liver tumors- (controls were subtracted from total observed in treated)								
Study, strain	Aroclor	Months	# males	# females	A+C/total M	C/total M	A+C/total F	C/total F
IBT (1971b), S-D	1254	23-24	35	35	0/11 (0%)	0/11 (0%)	1/14 (7%)	0/14 (0%)
IBT (1971a), S-D	1242	23-24	35	35	0/6 (0%)	0/6 (0%)	0/14 (0%)	0/14 (0%)
IBT (1971c), S-D	1260	23-24	35	35	0/10 (0%)	0/10 (0%)	0/15 (0%)	0/15 (0%)
Kimbrough, et al. (1975), Sherman	1260	23	0	184	-	-	26/184 (14%)	26/184 (14%)

Source: Eaton 2019.⁴

3.5.3. Number of Dose Groups

The following is FDA's summary of the dosing scheme for DDT. It refutes Dr. Eaton's statement that the number of dose groups pre-1970 was typically a single dose group. Clearly, FDA used more than one dose level in the 1947 Fitzhugh and Nelson study.² In fact, the FDA tested five dose levels and 12 rats per dose level (which was even more than the protocol suggested in the 1949 Black Book¹):

PART I. TWO-YEAR EXPERIMENTS.

Method. Two experiments were conducted in which groups of weanling rats (21 days) from our colony of Osborne-Mendel strain were started on diets containing a commercial preparation of DDT composed of 81.8% p,p isomer and 18.2% o,p isomer. In the first experiment, started early in 1943 when our supply of DDT was small, 5 groups of 12 male rats were fed on diets containing respectively 0, 100, 200, 400 and 800 p.p.m. DDT incorporated in a 10% corn oil solution.

Fitzhugh and Nelson continued their DDT cancer study to include an even greater number of animals:

In a second experiment, started about a year later, 7 groups of 24 rats, equally divided between the sexes, were fed on diets containing respectively 0, 200, 400, 600 and 800 p.p.m. DDT incorporated in a 10% corn oil solution, and 600 and 800 ppm. dry DDT for comparison with the oil solutions.

RESULTS. Since the second experiment involved a much larger number of animals than the first, the following discussion of results will be confined to the former except that mention will be made to any differences which occurred in the two experiments.

3.5.4. Animal Care

Contrary to Dr. Eaton's claims, animal housing, care, and observations were the same as we use in today's studies, with both body weights and food consumption closely monitored. Dr. Eaton stated that this was not standard practice until after 1970. Fitzhugh and Nelson state:²

All animals were kept in individual cages in a room with controlled temperature and humidity and were given free access to their respective diets and water. Body weights and food consumption were determined at weekly intervals.

The rats were closely monitored for any change in body weight since that is a sensitive indicator of toxicity, and this was FDA standard practice in 1943. (See 0.) The reason I included the FDA table is to show how standardized the careful monitoring of animal weights was by 1943 and that it was already recognized as a critical component of any chronic lifetime animal cancer study.

Exhibit 10. Table 1 from Fitzhugh and Nelson 1947: Weight Gain in Rats Fed Diets Containing DDT

TABLE 1 Mean gain in weight of rats fed diets containing DDT (second experiment)				
TIME	DOSAGE OF DDT	SEX	NO. OF ANIMALS	MEAN GAIN IN WEIGHT
months	0	M	11	310.2 \pm 13.3
		F	12	205.3 \pm 6.8
	200	M	12	300.8 \pm 9.5
		F	12	203.7 \pm 6.8
	400	M	12	316.6 \pm 5.3
		F	12	177.3 \pm 6.4†
	600	M	12	279.9 \pm 11.4
		F	12	178.8 \pm 60.0†
	{ 600 Dry	M	12	280.0 \pm 9.9
		F	10	176.7 \pm 4.1†
	800	M	12	273.7 \pm 14.8
		F	12	172.8 \pm 7.7†
12	0	M	10	486.6 \pm 18.9
		F	11	293.5 \pm 10.7
	200	M	9	488.1 \pm 26.5
		F	10	282.0 \pm 10.9
	400	M	10	537.8 \pm 24.2
		F	9	253.7 \pm 10.8*
	600	M	11	481.4 \pm 23.2
		F	5	240.4 \pm 14.9*
	{ 600 Dry	M	11	463.6 \pm 8.7
		F	3	238.7 \pm 4.4†
	800	M	10	473.7 \pm 21.0
		F	1	
	{ 800 Dry	M	6	459.8 \pm 12.9
		F	0	

* p < .05 - > .01.

† p < .01.

Source: Fitzhugh and Nelson 1947.²

I have presented the FDA 1947 table of rat weights to show how important this information is to a toxicologist and to show that it was obviously standard practice by that date. This is noteworthy because IBT did *not* consider weighing rats to be a standard operating procedure in the PCB cancer studies IBT conducted for Monsanto in 1971, which is in the post-1971 period defined by Dr. Eaton. Instead of carefully and routinely weighing the rats in the PCB studies, IBT simply waited until the completion of the study and just *fabricated* the animal weights

(Glenn Brown trial testimony from October 28, 1991;¹⁶ I discuss this further below). IBT presented this false information in its reports.

In addition, the FDA closely monitored the organ weights of liver, kidney, and spleen. This was FDA's standard practice in 1943, contrary to Dr. Eaton's opinion. (See Exhibit 11.)

Exhibit 11. Table 3 from Fitzhugh and Nelson 1947: The Effect of Chronic DDT Ingestion on Various Organ Weights

DOSAGE OF DDT	SEX	NO. OF RATS	MEAN WEIGHT (GRAMS PER 100G. OF BODY WEIGHT)		
			Liver	Kidneys	Spleen
p.p.m. 0	M	6	25.6 ± 2.9	6.6 ± 0.5	1.1 ± 0.2
	F	7	32.7 ± 3.5	7.4 ± 0.4	1.7 ± 0.3
100	M	4	32.2 ± 1.6	7.4 ± 0.5	1.6 ± 0.1
200	M	7	33.2 ± 2.6	6.3 ± 0.3	1.9 ± 0.2
	F	9	48.7 ± 3.8†	8.5 ± 0.4	2.1 ± 0.4
400	M	6	39.9 ± 2.9†	6.8 ± 0.2	1.4 ± 0.4
	F	7	42.7 ± 2.3*	8.3 ± 0.8	1.7 ± 0.4
600	M	7	41.4 ± 3.5†	8.5 ± 0.5*	2.0 ± 0.4
	F	4	67.3 ± 3.3†	9.1 ± 0.5*	2.3 ± 0.7
{ 600 Dry	M	5	44.1 ± 6.1*	8.5 ± 0.3*	1.3 ± 0.6
	F	4	60.6 ± 2.1†	9.2 ± 0.7*	1.8 ± 0.4
800	M	8	47.3 ± 3.7†	8.3 ± 0.4*	1.6 ± 0.2
{ 800 Dry	M	4	44.2 ± 1.5†	8.7 ± 0.5*	2.0 ± 0.3

* p. < .05 - > .01.
† p. < .01.

Source: Fitzhugh and Nelson 1947.²

I show this table because the increase in liver weight should have been considered one of the “triggers” (to use Dr. Eaton’s term) for Monsanto to conduct a similar cancer study for PCBs. The pathological descriptions of PCB- and DDT-damaged livers were very similar between the FDA DDT study of 1947 and the Drinker PCB studies from the 1930s. For example, the FDA notes that the DDT rat livers had approximately *doubled* in weight and had a *nutmeg appearance*.²

Perhaps the one outstanding gross change in the treated animals was the increased size of the liver, as shown in table 3. In about a fourth of the animals the liver had a “nutmeg” appearance, more frequent on the higher than on the lower dosage levels, and not seen in the controls.

Likewise, Bennett et al. (1938; part of the so-called Drinker Studies)¹⁸ showed a similar pathological effect with PCBs. The liver weight *doubled* and had a *mottled* appearance:

In all animals the livers were enlarged (33 to 90 percent). The average weight increase was 71 percent. They were also friable, pale yellow in color, and somewhat mottled.

Miller also noted that the primary target organ in PCB-treated rats was the liver (Miller 1944), but he provided no organ weights.¹⁸

3.5.5. Tissue Analysis

Dr. Eaton suggests that histopathological examinations pre-1970 were not comprehensive. Not true. FDA conducted pathological examinations on the following extensive and comprehensive list of organs in the 1947 DDT study:²

Paraffin-embedded sections stained with hematoxylin and eosin were routinely made of lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, testis, thyroid and (except in the 200 p.p.m. and control groups) hind leg muscles. Ovary and uterus were sectioned in about half the females, and parathyroids were encountered in about half the thyroid sections. Other structures such as lymph nodes, hind leg bones, and bone marrow, were sectioned in a moderate number of instances, about two dozen of each. Special stains for fat and for iron-containing pigment were done in a few instances.

Perhaps the most obvious *trigger* for Monsanto that should have prompted it to conduct PCB cancer studies in the 1940s (at minimum) was the finding of greatly increased liver weight together with the *specific* pathological lesions FDA described for DDT.

There is a similar and very striking pattern of liver damage reported in the Drinker studies in 1938 (Bennett et al. 1938) and Miller (1944).^{18,19} The FDA study reported that the

histopathological lesions included *hyperplasia* (synonymous with mitotic figures) and *hyalinization*:

The characteristic microscopic change in the liver was proportional to dosage level, although the lower grades of the change were generally present even at the lowest dosage level of 200 p.p.m., and in the first series at 100 p.p.m. The lesion consisted principally in hypertrophy and increased cytoplasmic oxyphilia of the centrolobular hepatic cells, plus increased basophilia and margination of the cytoplasmic granules, and a tendency to hyalinization of the remainder of the cytoplasm...Eleven other rats showed varying amounts of nodular adenomatoid hyperplasia; the nodules were generally of 1 to 3 mm. diameter, and were usually noted grossly as scattered yellowish foci.

Bennett et al. (1938) reported very similar findings for PCB-induced lesions. When they compared rats dosed with penta- and hexachloronaphthalenes, they reported only *an occasional liver* contained hyaline droplets. However, when they dosed another group of rats with the same penta- and hexachloronaphthalenes plus 10% PCBs, they reported the following:¹⁸

Hyaline droplets in the altered cytoplasm were a conspicuous feature (see fig. 3, plate III). Mitotic figures were present in abnormally large numbers.

Bennett et al. further reported that, although they tested mixtures of chloronaphthalenes and PCBs, there were dramatic increase in the pathological damage and hyalinization when just small amounts of PCBs were added to the mixtures. It is significant that they noted:

Feeding of tetra- and pentachloronaphthalenes in combination with chlorinated diphenyl resulted in pronounced liver changes...Microscopic examination revealed a peculiar type of hyaline degeneration involving practically every liver cell (see figs. 1 and 2, plate I). This type of cell degeneration was more marked and occurred earlier after exposure to preparations containing chlorinated diphenyl than to any other compounds tested. [emphasis added]

Miller (1944) also noted the presence of these *peculiar* round or oval intracellular bodies in rats after 60- and 90-day PCB exposures:¹⁸

In all of the rats receiving 10 such doses peculiar round or oval intracellular bodies were observed in the livers of the animals in both 60- and 90-day groups...These bodies varied considerably in size...It was hyaline and deeply

eosinophilic, with a scant basophilic outer margin, and sometimes presented a concentric lamination. The thickness of this hyaline shell varied.

Importantly, Miller found that hyalinization was not an acute lesion resulting from a single PCB dose but was only found with repeated exposures—likely due to bioaccumulation:

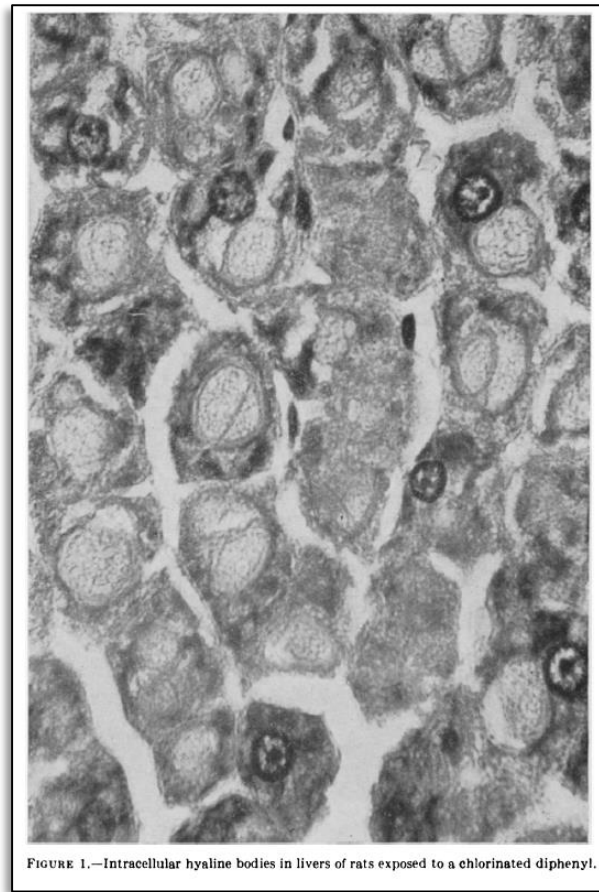
Intracellular hyaline bodies were found in the liver of the rat alone. They were present, usually in large numbers, in all of the rats receiving 10 0.05-cc. doses and in some of the animals receiving 25 doses by skin and corneal applications and ingestion, but were not observed in any of the animals subjected to single doses...None were observed in rats examined prior to 50 days on test.

Miller also confirmed my opinion that these hyaline bodies were rare. His findings were consistent with those of Bennett et al. (1938) and, therefore, could be used as hallmarks of chlorinated compounds:

These findings agree with Bennett [Bennett 1938] who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.

Miller apparently thought these hyaline figures so unique and specific for PCB-treated rats that he presented a single photomicrograph of these *peculiar* morphological structures in his publication (he showed no other photomicrographs). (See Exhibit 12.)

Exhibit 12. Figure 1 from Miller 1944: Intracellular Hyaline Bodies in the Livers of Rats Exposed to a PCB



Source: Miller 1944.¹⁹

The similarities between pathological lesions reported in the Drinker PCB studies (Bennett et al. 1938), the Miller study (1944), and the FDA DDT study (Fitzhugh and Nelson 1947) are obvious and unmistakable.^{2,18,19} Reading these three studies side-by-side, it is clear that there are many similarities between DDT and PCBs with regard to the specific lesions reported—particularly, the increased liver weight and the unique and peculiar hyaline bodies. The increased liver weight and the presence of hyaline bodies are hallmarks of tumorigenesis. What Drinker and Miller could not know is whether the early pathological lesions they were describing would progress to hyperplastic nodules or tumors that were later described by FDA in the 1947 DDT cancer study. The reason is simply that both Drinker and Miller were conducting subacute studies that were

terminated after only a few months. If they *had* conducted chronic, long-term cancer studies and continued their PCB dosing for the entire 2-year exposure in rats, I have little doubt that they would have found PCBs were carcinogenic even before the FDA showed in 1947 that DDT was carcinogenic.

3.6. Dr. DeGrandchamp Response to Dr. Eaton's Answer to Charge Question 4 (Dr. Eaton Report, Page 86)

Dr. Eaton was asked to consider whether an animal cancer test performed during the 1930s–60s would have shown that PCBs caused cancer in laboratory animals:

Charge 4: *Consider whether, if an animal test for cancer had been performed in the 1930's–60's, it would have demonstrated that PCBs cause cancer in laboratory animals.*

Dr. Eaton Response: *Had Monsanto found a laboratory willing and able to conduct a 'test for cancer' in the 1930s, 40s, or 50s, or established its own, it is highly unlikely that the study would have found a statistically significant increase in tumors from PCBs.*

Dr. Eaton states as his rationale:

- 1. They likely would have tested the animals for 18 months or less, as was typical of such studies of that time. (Dr. Eaton Report, page 86.)*
- 2. They likely would have used an insufficient dose and/or route of exposure. Nearly all of the toxicology studies done on PCBs in 1930s-1950s were focused on workplace concerns about toxicity following inhalation exposure. The pioneering work of Drs. Drinker and Treon never really considered ingestion as the principle 'route of exposure', although they did do some feeding studies that corroborated the liver as the primary 'target organ' for toxicity of the mixtures of industrial compounds they were studying. Rather, their focus was, appropriately at the time, on workplace exposure via the inhalation route. Had Dr. Drinker or others conducted a 2-year inhalation study of PCBs, it is extraordinarily unlikely that it would have produced an adequate dose to the liver to cause liver tumors, which is the primary form of reproducible, statistically significant tumor develop in rat bioassays of PCB mixtures. (Dr. Eaton Report, page 86.)*

3. *Had Monsanto decided to conduct an inhalation test for cancer, it would likely have used a laboratory such as Dr. Treon's laboratory. (Dr. Eaton Report, page 87.)*
4. *Of 27 different 2-year studies on various commercial mixtures of PCBs (some using only males or females, some using both sexes; see Table 4 on p. 34, see also Appendix 3), only 7 of the 27 studies (26%) identified a positive response for cancers (and two others had increases in benign adenomas)...This rat strain was not widely used prior to the protocol development effort of the Weisburgers in the early 1960s. (Dr. Eaton Report, page 88.)*

It is noteworthy that Dr. Eaton is rationalizing an excuse for why Monsanto did not conduct any 2-year cancer studies until 1969. Furthermore, he is stating that if Monsanto had conducted such studies, it would not have found evidence that PCBs were carcinogens. In all my reviews of the Monsanto memos and documents relating to Monsanto's "toxicity" studies, not one had made a similar excuse. Dr. Eaton's opinion that Monsanto did not conduct any 2-year cancer test because the cancer testing protocols were not standardized is undercut by Monsanto's own statements regarding when—and, more importantly, *why*—Monsanto initiated those very first IBT PCB 2-year cancer tests in 1969 (MONS213386).¹⁷ (See Exhibit 13.)

Exhibit 13. Excerpt from A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls

In 1969, Monsanto sponsored a series of animal studies at Industrial BIO-TEST Laboratories in Northbrook, Illinois, on Aroclor 1242, 1254, and 1260 for the assessment of the health and environmental hazards of these materials. This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice and a toxicity/reproduction study in chickens on each of the 3 Aroclor products. Even though no such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment. A report (Nelson, 1972b)

Source: Levinskas 1981.¹⁷

This quote is from a lengthy (70-page) Monsanto document: *A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies*, which was authored by Dr. George J. Levinskas in 1981 (MONS213336 to MONS 213405).¹⁷ He states that the only reason Monsanto initiated the IBT studies was because PCB had been detected in the environment.

Dr. Eaton states that Monsanto was not required by any FDA regulatory requirement under the 1938 FD&C law to conduct any toxicity testing. However, Dr. Eaton ignores the fact that Monsanto *did* conduct a broad battery of toxicity tests, including 2-year chronic feeding studies, for Aroclors 1242, 1254, and 1260 for just that purpose. That is, the IBT–Monsanto Aroclor cancer tests were conducted specifically to meet the requirements of the FDA regulation to “support Food Additive Petitions for each of these materials,” as stated by Monsanto’s Dr. George Levinskas.

This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice, and a toxicity/reproduction study in chickens on each of the three Aroclor products. Even though no

such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment.

As I have discussed, the FDA's 1949 Black Book was written so that the entire chemical industry would have standard protocols that would produce uniform study results. These were intended to provide a testing framework of consistency. They are, in fact, very similar to those toxicological testing protocols Levinskas was referring to in 1969.

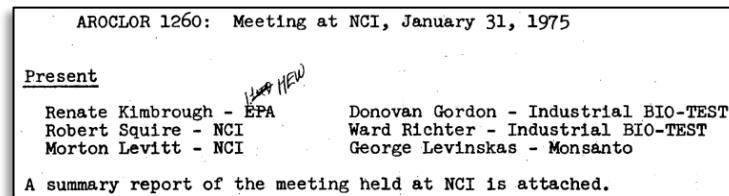
The above statements by Monsanto do not support Dr. Eaton's opinion that the *reason* Monsanto did not conduct 2-year cancer test is that there were no standardized protocols that Monsanto could have followed until 1970. It appears that either Dr. Eaton is *now* claiming that Monsanto did not perform a cancer test on PCBs because the science had not advanced to the point where such tests could be conducted or that, if Monsanto had conducted such tests, it would not have found that PCBs were carcinogenic.

While Dow, DuPont, and Bayer A.G. were testing their chemical products (in the late 1930s) for cancer before they were produced, Monsanto started its cancer testing *after* it had been manufacturing PCBs for 40 years. Simply put, Monsanto started chronic toxicity studies and cancer studies in 1969, and the reason was not because standard scientific protocols for conducting such tests did not exist.

Notwithstanding the fact that standard testing practices were available as early as 1949, Dr. Eaton's discussion of standard practice is *irrelevant* to my opinion. My opinion is that there were at least 50 solid studies that described robust cancer testing methods by 1950. The only issue I address is whether scientific sources of cancer testing information were available and whether a good and robust study design had been developed. If Monsanto had truly been interested in conducting a cancer study in the early 1940s, it needed only to contact the NCI or FDA, both of which employed many cancer experts. Industrial and academic scientists reach out for guidance or to discuss scientific matters on a routine basis. This is just a generally practiced part of scientific collaboration. I have personally contacted many governmental scientists during my approximately 30 years in toxicology practice and have likely had 50 to 100 extensive conversations to acquire knowledge I did not have regarding diverse scientific matters. Even the

Monsanto memos and documents show Monsanto frequently met with governmental officials to discuss *scientific issues*. For example, based on my review of Monsanto memos and documents, Monsanto convened a meeting between U.S. EPA (HEW), NCI, IBT, and Monsanto in 1975 to discuss cancer findings of PCB studies.²⁰

Exhibit 14. Excerpt from Aroclor 1260 Meeting at NCI



Source: Levinskas 1975.²⁰

Monsanto did not function as a scientific island. It was a major chemical company that could have chosen among hundreds of experts in the cancer testing field. The massive amounts of PCBs Monsanto was producing would have warranted the expenditure of funds for those studies.

In addition to talking to the FDA, Monsanto could have simply adopted the FDA 1949 cancer study for DDT (Fitzhugh and Nelson 1947)² and found positive and unmistakable signs of cancer. Dr. Eaton summarizes the state-of-the science without even *citing* (let alone considering) the FDA DDT 1947 study or the 1949 FDA Black Book (Lehman et al. 1949),² both of which detail how chronic cancer testing should be conducted. As I previously indicated, the FDA specifically states that its guidance should be used for chemicals that are likely to contaminate foods (based on the massive amounts of PCBs manufactured, this could have been predicted). This is clearly stated in the FDA Black Book Discussion and Summary: ²

Discussion and Summary

Arnold J. Lehman [Chief, Division of Pharmacology, Food and Drug Administration]

The body of knowledge accumulated as the result of the above described studies has for its purpose the determination of the relative safety of the chemicals proposed for addition to foods or likely to contaminate foods.”

Nevertheless, I have been requested to consider Dr. Eaton’s rationale for why Monsanto *would not* have found that PCBs were carcinogenic in animal tests. Before addressing each of Dr. Eaton’s reasons, it is very important to stress that even the very first study IBT conducted for Monsanto showed PCBs *were* carcinogenic, which the company admitted in numerous documents. This is not my opinion; it is a fact *specifically stated in numerous* Monsanto documents. This fact is diametrically opposed to Dr. Eaton’s opinion. Despite there being numerous documents stating this fact, none of these Monsanto documents are included in Dr. Eaton’s report; Dr. Eaton appears to have chosen to ignore these documents for an unexplained reason. It should also be noted that, after completion of the IBT–Monsanto PCB studies, Monsanto attempted to falsely change IBT’s conclusions. Furthermore, Monsanto devised a path forward to outmaneuver other cancer scientists in an attempt to publish IBT’s fraudulent and false cancer studies before they could.

The following is a summary of facts regarding Monsanto’s own IBT cancer studies, which rebut Dr. Eaton’s opinion that those 1971 studies *did not* show PCBs were carcinogenic (when they clearly did):

1. IBT completed the Monsanto 2-year Aroclor cancer tests in 1969. Despite the fact that IBT falsified its reports by replacing dead animals with new animals (among other egregious practices), IBT pathologists still concluded at the end of the study that PCBs *were carcinogenic*.
2. While IBT, CDC, and NCI scientists all concluded Aroclors were carcinogenic, Monsanto argued that PCBs did not cause “malignant” tumors, so they were not carcinogenic. Dr. Eaton is relying on the same discredited and false definition of carcinogenic compounds in his opinion.

3. Monsanto directed IBT to falsify conclusions about whether Aroclors were carcinogenic and to change the cancer classification of PCBs.

Brief descriptions of each of the above issues are in the following sections.

3.6.1. IBT's PCB Studies Proved Aroclors Were Carcinogenic

After IBT completed the Aroclor cancer studies in early 1970, the CDC's Dr. Renate Kimbrough had also just completed an independent cancer study showing that Aroclor 1260 was carcinogenic. IBT decided to review her study and compare her results with its own Aroclor 1260 cancer study. IBT issued a report on the comparison titled, *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458); IBT concurred that Aroclors were carcinogenic.²¹

Monsanto states that Dr. Kimbrough's histopathological examination showed that 170/180 rats developed neoplastic "nodules" and "hepatocellular carcinomas:"

It was therefore concluded that Aroclor 1260 has a hepatocarcinogenic effect in female Sherman strain rats.

The Monsanto document goes on to state that IBT's own pathologist Dr. Gordon came to the same conclusion:

Another study in albino rats with Aroclor also showed inconclusive results; while no carcinogenic response could be observed in a preliminary study, Dr. Gordon (Bio-Test Laboratories Inc.) reported a slight tumorigenic property of Aroclor 1242, 1254, and 1260 in rats were fed continuously at levels of 100 ppm for 2 years.

Exhibit 15 presents the number of carcinogenic lesions in PCB-treated rats versus control rats from the IBT Aroclor 1260 reevaluation study. IBT confirmed that Aroclor 1260 was carcinogenic, with results similar to those of the Dr. Kimbrough's CDC study (the comparative study prompting IBT's reevaluation). The IBT pathologist reported that 179/184 rats developed evidence of carcinogenicity (hyperplastic nodules), which was very similar to Dr. Kimbrough's tally of 170/180 rats showing the same pathology. Despite these very high rates of

carcinogenicity in both the IBT and Kimbrough studies—and the admission by the IBT pathologist who examined the tissues that PCBs were carcinogenic—Dr. Eaton claims the IBT studies *did not* show evidence of cancer.

Exhibit 15. Table 21 from Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260

Table 21: Differences of liver lesions in control and experimental rats treated with Aroclor 1260		
	Experimentals	Controls
Vacuolization	155	13
Focal granular alteration	100	31
Single granular alteration	169	45
Single cell necrosis	125	17
Group cell necrosis	36	2
Cell enlargement	175	17
Ductal proliferation	52	3
Cholangiomatous lesion	7	-
Stern cell proliferation	121	87
Hyperplastic nodules:		
without atypia	136	9
with atypia	43	1

Source: *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458).²¹

I have previously discussed hyaline bodies or inclusions as unique pathological features that should have been seen by Monsanto as triggers that prompted the company to conduct cancer studies in the 1930s or 1940s because they were reported as important PCB-induced lesions by both Drinker (1938) and Miller (1944).^{19,22} Hyaline bodies were also described in the FDA DDT cancer study (Fitzhugh and Nelson 1947) as developing during tumorigenesis.² The relevance and importance of these pathological features is that they were also described by Monsanto as being among the prominent pathological lesions in its cancer studies (Exhibit 16). IBT reports that the hyperplastic nodules contained “inclusion bodies” with “lamellated PAS-positive materials” (which is synonymous with hyaline bodies).

Exhibit 16. Excerpt from Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260

Hyperplastic nodule without atypia: This lesion was characterized by circumscribed areas of large hepatocytes (2-8 times larger than regular liver cells) showing mostly foamy, light eosinophilic, sometimes also basophilic cytoplasm occasionally with inclusion bodies (bile pigment, concentric lamellated or fibrillar structures, PAS-positive materials). These foci, in part corresponding to lesions termed "neoplastic nodules" by Dr. Kimbrough, usually occupied an area of the size of several lobules and were well-demarcated, partially suggesting

Source: *Report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS 043458).²¹

3.6.2. While IBT, CDC, and NCI Scientists All Concluded Aroclors Were Carcinogenic, Monsanto Argued that PCBs Did Not Cause "Malignant" Tumors, So They Were Not Carcinogenic

IBT, CDC, and NCI all agreed that the correct classification of a carcinogen is based on both benign and malignant pathological evidence. Monsanto asserted that PCBs should not be classified as carcinogens because they did not produce malignant tumors that metastasized (malignant tumors were never the definition of carcinogenicity). Dr. Eaton is relying on the same discredited histopathological criteria that Monsanto claimed in the 1970s, only to be corrected by the NCI consensus statements presented in Report of a Workshop on Classification of Specific Hepatocellular Lesions in Rats (Squire and Levitt, 1975).²³ The workshop, consisting of 20 experts in pathology and experimental carcinogenesis met for 2 days (December 11–13, 1974) to establish standardized terminology and criteria to identify tumorigenic pathological lesions. The NCI's role in such standardization was clearly defined:

The Carcinogenesis Bioassay Program of the National Cancer Institute has broad responsibility for detecting environmental carcinogens and depends upon the evaluation of specific tumor diagnoses by the National Cancer Institute and collaborating scientists throughout the country. Of prime importance in many of the results is the interpretation of proliferative lesions of rodent livers. It is vital

to the goals of the Program that these lesions are properly classified and a nomenclature agreed upon.

Squire and Levitt summarized the participants' consensus pathological criteria and nomenclature in Exhibit 17. It is noteworthy that this was the same classification scheme used by CDC, NCI, and IBT in their pathological evaluation of the PCB cancer studies in which the "Foci of cellular alteration" were included as important criteria. That is, both Dr. Kimbrough and IBT identified carcinogenic changes in Aroclor-treated animals consistent with the recommended classification scheme shown below. Monsanto disagreed with Dr. Kimbrough and its own consultant (IBT).

Exhibit 17. Table 1 from Squire and Levitt: Classification of Hepatocellular Lesions in Rats

Table 1	
<i>Recommended classification of specific hepatocellular lesions in rats</i>	
I. Foci of cellular alteration	
A. Clear cell foci	
B. Eosinophilic or ground glass foci	
C. Basophilic foci	
D. Mixed cell foci	
II. Neoplastic nodules	
III. Hepatocellular carcinomas	
A. Well differentiated	
B. Moderately differentiated	
C. Poorly differentiated	
D. With glandular and/or papillary formation	
IV. Cholangiofibrosis	

Source: Squire and Levitt 1975.²³

Contrary to Monsanto's discredited classification scheme, in which clear evidence of tumor malignancy was necessary, the NCI stated that foci of cellular alteration (which are not evidence of malignancy or metastasis) are important criteria because they may be a part of the "spectrum capable of processing to the formation of nodules." This specific rational succinctly stated by NCI is the same criteria I applied and relied on to conclude that, based on my evaluation of the Drinker (Bennett et al. 1938) and Miller (1944) studies, the lesions were consistent with the same lesions the NCI explained to be the spectrum of histological changes that could proceed to nodules and then into tumors.^{18,19} Drinker and Miller identified the early pathological hallmarks

that could represent tumorigenesis (as stated by NCI). I did not opine that I was certain they would process into tumors. Because they were the characteristic hallmarks of cancer that are seen in the early stage (that were well-known at the time), the presence of these lesions should have been a trigger for Monsanto to confirm or negate that PCBs were carcinogenic. Drinker and Miller could not have known that PCBs were carcinogenic at the time because both experiments lasted only about 3 months. However, the IBT PCB cancer studies and most of the other cancer studies did confirm that the early hallmarks I described in my expert report were consistent with the NCI classification of early tumor formation. That is, they were part of the spectrum that progressively (with continued PCB exposures) leads to carcinogenic effects. Dr. Eaton states that my opinion is incorrect, despite the fact that all cancers develop gradually during tumorigenesis. Cancer does not simply suddenly appear overnight.

As noted, the NCI classification workshop developed *consensus* among all cancer experts (which is often rare) regarding the appropriate pathological criteria and nomenclature to describe the pathological manifestation of carcinogenesis. Despite the scientific consensus of the leading cancer researchers of the time, Monsanto continued to disagree with the NCI classification scheme because no actual *malignant tumors* were detected in the PCB cancer studies.

Because the NCI pathological classification scheme would obviously have major ramifications for considering Monsanto's Aroclors safe and nontoxic if they were classified as carcinogens, Monsanto convened a scientific meeting between CDC (Dr. Kimbrough), NCI, IBT (Dr. Gordon, Section Head, Pathology), cancer experts, and Dr. Levinskas from Monsanto on January 31, 1975, to discuss the classification scheme and to also allow the experts from all three groups to microscopically review the rat liver tissues from PCB-treated animals.²⁰ Dr. Kimbrough and IBT had completed their cancer studies of Aroclor 1260, and extensive pathological examinations were conducted for the two studies. The goal was two-fold. The first was to reach consensus among the experts that the NCI classification was being appropriately applied to PCB-treated rat livers. The second was to make a side-by-side *comparison* between the Dr. Kimbrough and IBT study microscope slides to determine if the CDC and IBT pathologies were the same.

Dr. Levinskas also wrote a summary memo (STLCOPCB4052173) for the meeting attendees (CDC, NCI, IBT, and Dr. Levinskas) that captured the scientific discussion and conclusions

based on the actual microscopic histopathological examination of the type and quantity of carcinogenic lesions in Aroclor 1260 rat livers from the CDC and IBT studies, on which they reached consensus. More importantly, however, was the side-by-side examination of CDC and IBT rat liver histology studies. According to Monsanto's own notes, CDC, NCI, and IBT pathologists all agreed that the CDC and IBT study results were essentially the same. Monsanto's Dr. Levinkas summarized his conclusions, making the three important points, as presented in Exhibit 18.

Exhibit 18. Excerpt from Aroclor 1260: Meeting at NCI, January 31, 1975

1. In our earlier study, the severity of liver lesions was greater in females than in males.
2. To a large extent, substantially the same type of lesions were observed in both studies ~~except that the lesions seemed to be more advanced in Kimbrough's study. Although there was some variation in terminology, the findings were reasonably close.~~
3. ~~There were definite liver adenocarcinomas in Kimbrough's study. Dr. Richter expressed the view later that 2 animals in our study approached the type of lesion Kimbrough had observed, but there was agreement by Drs. Gordon and Richter that Dr. Kimbrough's rats had developed a lesion which they had not observed in our earlier study with AROCLOR 1260.~~

Source: Levinkas 1975.²⁰

Dr. Levinkas's summary memo (STLCOPCB4052173) was sent to all attending meeting experts, and they were invited to respond to Dr. Levinkas if they felt his memo incorrectly summarized the scientific consensus of the meeting.

Despite, what appears to be a straightforward summary of the meeting sent to the attendees, however, Dr. Levinkas wrote another internal summary memo for Monsanto management that makes it clear Monsanto was not pleased with the outcome.²⁰ Dr. Levinkas was clearly hoping that there would be a different conclusion, given that IBT's pathologist attended the meeting. That hope was dashed because the IBT pathologist concurred with CDC and NCI experts, with all concluding that Aroclor 1260 was a carcinogen. Furthermore, in discussing Dr. Kimbrough's

Aroclor 1260 findings that showed it was a carcinogen in her study, Dr. Levinskas himself had to conclude that her results were hard to refute. He came to this conclusion even though Dr. Kimbrough did not have any data on “spontaneous tumor rates” in untreated rats from her study.

Control animals in this study had very “clean” livers. The incidence of spontaneous changes was quite low. Insofar as could be determined, Dr. Kimbrough has no data from other 2-year studies which could be used to assess the spontaneous tumor incidence of this strain of rat. Despite the absence of historical control data, her results would be hard to refute.

Dr. Levinskas’s statement is important for two reasons. First, Monsanto concluded that Dr. Kimbrough’s study and conclusions were scientifically valid because it presented overwhelming evidence of PCB-induced carcinogenicity. Second, Monsanto’s acceptance of Dr. Kimbrough’s results indicates that Dr. Eaton is not correct in stating that a laboratory must have historical evidence of spontaneous tumor rates and that this was a standard practice post-1970, as he states in Table 12 from his report.

In the internal memo, Dr. Levinskas (Monsanto) goes on to state that he was only an observer and he was unable to “caucus” with IBT’s pathologist during the meeting with Dr. Gordon. Dr. Levinskas states:

After we left, and they [presumably, IBT’s Dr. Gordon] conceded to the occurrence of hepatic carcinomas, there was little else to do. I got the impression that Dr. Kimbrough plans early publication of her findings. [emphasis added]

Failing in the effort to alter, modify, or change the conclusions of CDC, NCI, or IBT based on the actual scientific findings and merits of the reexamination of the rat liver tissue, Monsanto had little recourse. Consequently, Dr. Levinska’s plan on how to proceed was to:

...publish our 2-year study on AROCLOR 1260 before Dr. Kimbrough gets into print. This would at least blunt the impact of her study.

It is not clear from Dr. Eaton’s report that he has reviewed these Monsanto’s memos or if they were part of his reliance materials. However, it is clear that by 1975, the IBT cancer studies were consistent with other independent cancer studies in proving Aroclors were carcinogenic.

Based on all of the above facts and information, Dr. Eaton's Table 4 is incorrect, and his conclusions regarding Aroclor-induced cancer in laboratory animals is not credible. I show part of his Table 4, which is incorrect for two reasons. First he shows that Monsanto's own IBT studies were not positive for cancer, I have disputed that a thorough review of both IBT's *Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260* (MONS043458) and Dr. Levinskas own admission that CDC, NCI, as well as IBT's pathologist reached consensus Aroclor 1260 was carcinogenic. This part of his table is incorrect. Secondly, Dr. Eaton's table while correctly showing that the Kimbrough study was positive for cancer the IBT studies were negative even though Dr. Levinskas admitted that the consensus among CDC, NCI, and IBT experts was that Dr. Kimbrough's and IBT's study results were "substantially the same." If the studies were substantially the same it would not be possible to have one study negative for cancer while the other is positive.

Exhibit 19. Table 4 from Dr. Eaton Report: Summary of 2-Year Carcinogenicity Bioassays Completed on Commercial Mixtures of PCBs, 1971, 1972, 1974, and 1975

Table 4. Summary of 2-year carcinogenicity bioassays completed on commercial mixtures of PCBs						
Year	Species and strain	Test group numbers	Dose groups (ppm)	PCBs studied	Positive for cancer (M, F)*	Reference
1971	CR Albino rats; males and females	8 groups; 50 per group	0, 1, 10, 100	Aroclor 1242	No, No	(IBT, 1971a)
				Aroclor 1254	No, No	(IBT, 1971b)
				Aroclor 1260	No, No	(IBT, 1971c)
1972	Dd mice	4 groups; 6-12 per group	0, 100, 250, 500	Kanechlor 300	No	(Nagasaki <i>et al.</i> , 1972)
				Kanechlor 400	No	(Ito <i>et al.</i> , 1973a; Ito <i>et al.</i> , 1973b)
				Kanechlor 500	Yes	
1974	Male Wistar rats	4 groups, 10-25 per group; fed for 1 yr	0, 100, 500, 1000	Kanechlor 300	No	(Ito <i>et al.</i> , 1974)
				Kanechlor 400	No	
				Kanechlor 500	No	
1975	Female Sherman rats	2 groups, 200 per group	0, 100	Aroclor 1260	Yes	(Kimbrough <i>et al.</i> , 1975)

Source: Eaton 2019.⁴

3.6.3. Monsanto Directed IBT to Falsify Conclusions about Whether Aroclors Were Carcinogenic and to Change the Cancer Classification of PCBs

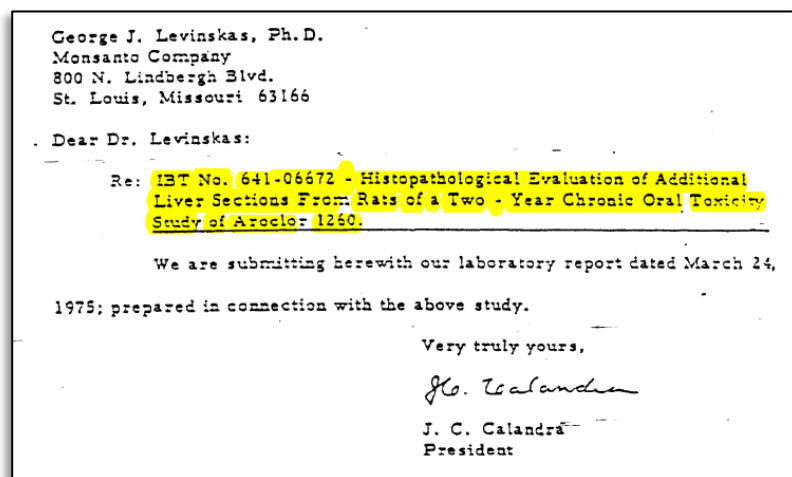
By 1975, consensus was reached between CDC, NCI, and IBT pathologists that Aroclors were carcinogenic in long-term animal studies (STLCOPCB4052174). Despite this development, Monsanto continued to pressure IBT to misrepresent the conclusions. As I discussed in my expert report (page 69), despite IBT's stated results and conclusions that Aroclors were carcinogenic, Monsanto continued to coerce and force IBT to change the cancer classification for Aroclors.

In addition to the evidence I have already discussed in my expert report, the document presented in Exhibit 20 through 0 should also be considered evidence of Monsanto's efforts to mislead CDC and NCI scientists about the carcinogenicity of Aroclor 1260, as it is relevant to the above facts and discussion. This document is a cover letter from Dr. Calandra (President of IBT) to Dr. Levinskas (Monsanto) that was attached to the IBT report: *Two-year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections*, March 24, 1975.²⁴ This document is important for four reasons:

1. The date it was sent;
2. Who it was sent to at Monsanto;
3. Who signed the report; and
4. That the carcinogenic classification was deliberately and falsely changed from “slightly carcinogenic” to noncarcinogenic.

While I discussed the letter sent by Monsanto forcing IBT to change the classification in my expert report, I have since reviewed the sequence of scientific meetings that preceded that letter. First, this cover letter with attached report was dated March 24, 1975, which was approximately 2 months *after* the January 31, 1975, expert meeting convened by Dr. Levinskas (Monsanto) with CDC (Dr. Kimbrough) and NCI experts, and IBT pathologist Dr. Gordon in which all experts concurred, along with Dr. Levinskas (Monsanto) that Aroclor 1260 was carcinogenic.

Exhibit 20. Cover page from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



Source: Calandra 1975.²⁴

The summary of the report indicates that a reexamination of the PBC rat liver tissues showed Aroclor 1260 was *slightly tumorigenic*. This document was signed by IBT's Dr. Gordon and sent to Dr. Levinskas.

**Exhibit 21. March 24, 1975, Summary from Report to Monsanto Company:
Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino
Rats; Histopathological Evaluation of Additional Liver Sections, March
24, 1975**

II. Summary

In most instances, the treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were three benign liver tumors detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 appears to be slightly tumorigenic at levels of 100 ppm when fed continuously in the diet for two years.

Respectfully submitted,
INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by: D.E. Gordon
D.E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: M.L. Keplinger
M. L. Keplinger, Ph.D.
Manager, Toxicology

DSW 036629

Source: Calandra 1975.²⁴

However, another document was prepared that stated Aroclor 1260 was *not* carcinogenic. Both documents are signed by Dr. Gordon (with what appears to be the identical signature).²⁴ Since this document was sent approximately 2 months after CDC, NCI, and IBT (Dr. Gordon) reached consensus that Aroclor 1260 was carcinogenic, Dr. Gordon knew in March, 1975, that this conclusion was false. He intentionally produced this document to mislead governmental

scientists; obviously Dr. Levinskas knew that as well, since he organized and participated in the March 1975 meeting.

**Exhibit 22. March 24, 1975, Conclusion from Report to Monsanto Company:
Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino
Rats; Histopathological Evaluation of Additional Liver Sections, March
24, 1975**

In conclusion, Aroclor 1260 appears to be slightly tumorigenic at levels of 100 ppm when fed continuously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

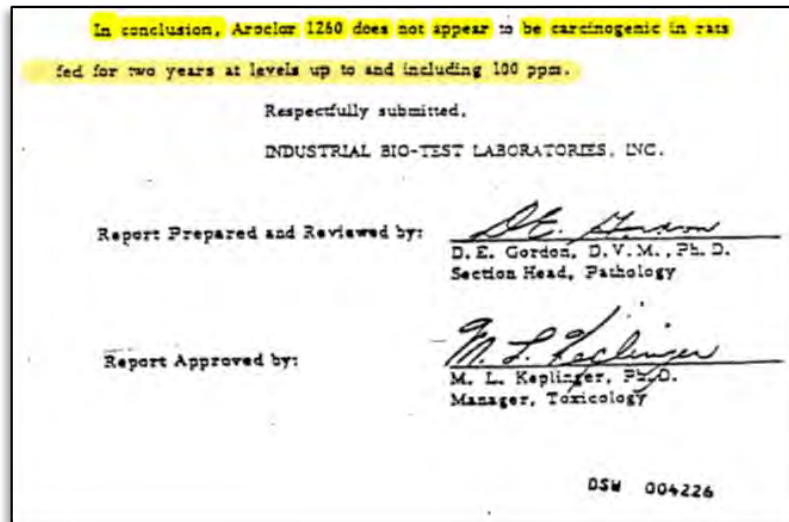
Report Prepared and Reviewed by: D. E. Gordon
D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: M. L. Keplinger
M. L. Keplinger, Ph.D.
Manager, Toxicology

QSW 030029

Source: Calandra 1975.²⁴

Exhibit 23. Final Page from Report to Monsanto Company: Two-Year Chronic Oral Toxicity Study with Aroclor 1260 in Albino Rats; Histopathological Evaluation of Additional Liver Sections, March 24, 1975



Source: Calandra 1975.²⁴

Dr. Levinskas also noted in his review compendium (MONS213337) that the BIO-TEST Laboratories had been challenged and that an evaluation of experimental protocol and data from the Aroclor 1242, 1254, and 1260 IBT studies were carried out, revealing significant discrepancies.¹⁷ He noted specifically that “The review showed that the data bases (including a lack of protocol) were insufficient for a complete validation of the study.”

Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a, b, c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals.

Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers.

This statement by Monsanto also undercuts Dr. Eaton's claim that post-1970, testing protocols were standard practice. As stated in Monsanto's own document, the IBT studies did not even have a formal experimental protocol.

On Page 86 of Dr. Eaton's expert report, he lists four reasons for the following statement:

Had Monsanto found a laboratory willing and able to conduct a 'test for cancer' in the 1930s, '40s, or 50s, or established its own, it is highly unlikely that the study would have found a statistically significant increase in tumors from PCBs.

The following sections rebut his opinions.

3.6.4. Dr. Eaton Point 1: They Likely Would Have Tested the Animals for 18 Months or Less, as Was Typical of Such Studies of that Time (page 86)

Dr. Eaton's term *typical* is not defined, and he does not discuss how he concluded that the more than 1,000 cancer studies that were published by the end of 1949 "typically" only lasted 18 months or less. This is a completely unsubstantiated statement and is in contrast to my opinion that most robust cancer studies were chronic dosing studies lasting a full 2 years or longer. However, if the studies he is referring to are studies in which tumors were found by 18 months, then it would be perfectly correct to terminate the study because it would have been successful. That is, the sole purpose of a cancer test is to determine if a chemical is a carcinogen; when tumors are identified prior to 2 years, it would be a waste of funds to continue the study.

Dr. Eaton is again misrepresenting the standard accepted practice of toxicology and constructing a false framework about whether Monsanto *could* have and *should* have proceeded with developing a cancer testing protocol for PCBs. It is not clear why Dr. Eaton continues to focus on typical practices in the 1930s–1960s when he has, in fact, not actually provided any evidence of what typical means—but that is irrelevant to this case. There was a very easy, cost-effective, and scientifically tenable cancer testing protocol that Monsanto could have developed that would

have had the added benefit of the imprimatur of governmental approval if Monsanto had simply chosen to follow the FDA standard protocol for testing DDT that was published in 1947.² This would have been easy because Monsanto would not have had to review the methods from more than 1,000 published studies, cost-effective because it would spend no time with pilot studies, and scientifically tenable because it was proven to be a good method for identifying carcinogens because the FDA had already used it to classify DDT as a carcinogen.

Dr. Eaton is also incorrect that studies were *typically* tested in chronic studies for *18 months or less*. This is easily disproven. The 1949 FDA Black Book clearly states that *all chronic rat studies are 2-year lifetime studies* (this alone proves Dr. Eaton's statement regarding what was typical is irrelevant).¹

3.6.5. Dr. Eaton Point 2: They Likely Would Have Used an Insufficient Dose and/or Route of Exposure. Nearly All of the Toxicology Studies Done on PCBs in 1930s–1950s Were Focused on Workplace Concerns about Toxicity Following Inhalation Exposure (Page 86)

This statement is incorrect for numerous reasons. Most importantly, he mischaracterizes the routes of exposure in early PCB studies:

- Dr. Drinker's study specifically did include ingestion, despite the fact that his study was a "cause of death study" in the workplace;²² and
- Dr. Miller's study, which is the best and most comprehensive PCB toxicology study that was published before the 1970s is not even cited in Dr. Eaton's supporting rationale. Dr. Miller also included the route of ingestion in his study design.¹⁹

Furthermore, the studies that Monsanto should have been using include the following:

- The FDA Black Book 1949 was specifically prepared for the chemical industry to standardize testing methods for chemicals that could contaminate food, which solely focused on contaminant ingestion.
- The FDA DDT 1947 study was only based on ingestion.²

Dr. Eaton's following statement highlights the major problem I have addressed in my expert report:

Nearly all of the toxicology studies done on PCBs in 1930s-1950s were focused on workplace concerns about toxicity following inhalation exposure.

This is not factually correct. Nevertheless, it is telling because it points out that Dr. Eaton's concern is that exposures in the workplace should have been the foremost concern for Monsanto, not the general public exposed to PCBs.

3.6.6. Dr. Eaton Point 3: Had Monsanto Decided to Conduct an Inhalation Test for Cancer, It Would Likely Have Used a Laboratory Such as Dr. Treon's Laboratory (page 87)

Dr. Eaton's comment is baseless and without merit. First, Dr. Treon was not an expert in cancer. Second, there were excellent academic, industrial, and governmental cancer testing laboratories. Third, I have reviewed the "Treon studies," and my opinion is that they are some of the worst-designed toxicity studies I have ever reviewed, and I have likely reviewed about 2000 studies in my toxicology practice. The Treon studies provide little relevant information about the toxicity of PCBs.

While Dr. Eaton relies on the Treon studies for his opinion, it is not credible for a scientist to use a single animal and conclude anything from that result, which the Treon study does. In fact, Dr. Eaton highlights the fact that the Treon studies used ridiculously few animals, but states that Monsanto would likely have given the task of conducting cancer studies to that laboratory (which is illogical). It is noteworthy that one of Dr. Eaton's opinions is that many of the pre-1970 early cancer studies did not use enough animals, but he is relying on the Treon study that used a single animal or two cats.

3.6.7. Dr. Eaton Point 4: Of 27 Different 2-Year Studies on Various Commercial Mixtures of PCBs (Some Using Only Males or Females, Some Using Both Sexes; See Table 4 on p. 34, See Also Appendix 3), Only 7 of the 27 Studies (26%) Identified a Positive Response for Cancers (and Two Others Had Increases in Benign Adenomas)... There Are Also Obvious Strain Differences in Rats, with Female Sprague Dawley Rats Showing, by Far, the Most Sensitive Response. This Rat Strain Was Not Widely Used Prior to the Protocol Development Effort of the Weisburgers in the Early 1960s.

Dr. Eaton is incorrect that only 7 of the 27 studies showed signs of cancer. The number of studies he states showed cancer is based on a misstatement of the pathological criteria for identifying evidence of carcinogenesis, as I have discussed. I provided the U.S. EPA summary of cancer tests performed that they considered relevant and pertinent to their classification. Both benign and malignant tumors were considered evidence of carcinogenicity based on the December 1974 NCI workshop (Squire and Levitt 1974).²³ The introduction states that the purpose was to classify the histopathology evidence of carcinogens:

On December 11 to 13, 1974, The National Cancer Institute sponsored a workshop in Silver Spring, Md. on the classification of hepatocellular tumors and related lesions of rats. There were 20 participants with extensive and varied experience in pathology and experimental carcinogenesis.

It is the responsibility of the NCI to establish clear standards and guidelines for carcinogens, as stated in the report:

The Carcinogenesis Bioassay Program of the National Cancer Institute has broad responsibility for detecting environmental carcinogens and depends upon the evaluation of specific tumor diagnoses by the National Cancer Institute and collaborating scientists throughout the country. Of prime importance in many of the results is the interpretation of proliferative lesions of rodent livers. It is vital to the goals of the Program that these lesions are properly classified and a nomenclature agreed upon.

Dr. Eaton appears to be imposing his own ad hoc criteria for pathological carcinogenicity that are contrary to, and fall well short of, the 1975 NCI classification presented previously (Exhibit 17).

Neoplastic nodules, which are considered the insipient stage leading to cancer, were defined as evidence of carcinogenicity. NCI states:

The nature of these lesions is controversial. Nevertheless, several participants felt that the basophilic foci or areas had greater significance with respect to tumor development than did the other cellular alterations. Most participants agreed that foci or areas were cytologically similar to the cellular elements of neoplastic nodules and may be part of the spectrum capable of progressing to the formation of nodules.

In Dr. Eaton's opinion, foci of cellular alterations, which were clearly identified as carcinogenic evidence, were disregarded. The NCI's statement simply means that benign early evidence of hyperplastic changes are in themselves evidence of a carcinogen.

According to the U.S. EPA:

Of the 3 studies with PCBs having an average chlorine content of 60%, one reported hepatocellular carcinomas (Kimbrough, et al. 1975) and 2 did not (Levinskas, 1981 and Weltman and Norback, 1978). Since Kimbrough, et al (1975) and Levinskas (1981) both used Lot No AK-3 of Aroclor 1260, the different conclusions they reached are not related to differences in the test material. In addition to the use of a different strain of rat, Kimbrough, et al. (1975) used a different histologic diagnostic criteria. Kimbrough, et al. (1975) used the criteria for classification of specific hepatocellular lesions in rats developed at a National Cancer Institute Workshop (Squire and Levitt, 1975). That workshop recommended that the term "neoplastic nodules" replace so-called "hyperplastic nodules" because "Such nodules are proliferative lesions...(PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures 1996)

3.7. Dr. Eaton Is Incorrect with Regard to the Number of Animal Cancer Studies Positive for Carcinogenicity

1. Dr. Eaton is incorrect that only 7 of the 27 studies showed signs of cancer. The number of studies he states showed cancer are based on a misstatement of the pathological criteria for identifying evidence of carcinogenesis as I have discussed. I provided the U.S. EPA summary of cancer tests performed that they considered relevant and pertinent to their classification. Both benign and malignant tumors were considered evidence of carcinogenicity based on the December 1974 NCI workshop: Report of a Workshop on Classification of

Specific Hepatocellular lesions in Rats (Squire and Levitt 1974) as I have discussed.

2. Dr. Eaton states that Sprague Dawley are particularly responsive to PCBs and that they were not widely available until 1960. The fact is that Sprague Dawley breed was one of the first colonized strain created by R. W. Dawley in 1925 (available at: <https://www.janvier-labs.com/rodent-research-models-services/research-models/per-species/outbred-rats/product/sprague-dawley.html>) so clearly they could have been used as early as the 1930's. However, Dr. Eaton ignores the fact that the
3. Dr. Eaton is incorrect by stating that the Sprague Dawley rat is the most sensitive and would not have been used in early PCB cancer studies. The fact is, the very first PCB cancer studies I discussed previously showed that neither the Kimbrough study nor the IBT studies used Sprague Dawley rats and the number of rats in Dr. Kimbrough's study showing carcinogenic lesions was 170/180 and this was closely matched the IBT study in which 179/184 had similar lesions (as was confirmed by IBT and Monsanto). While Dr. Kimbrough used the Sherman strain of rat, IBT used the Charles River CD strain both studied found that more than 90% of the rats showed pathologic carcinogenic lesions.
4. Dr. Eaton's opinion is based on an easily disproven incorrect assumption simply based on the high rate of animals that developed cancer in which the test animal was not a Sprague Dawley rat.
5. While Dr. Eaton is correct in concluding that not all PCB cancer studies show the same result with the exact number of animals showing carcinogenic effects, this is not a surprising result to most toxicologists. Indeed, it is to be expected. Although most toxicologists would agree that cigarette smoking causes cancer, not everyone who does smoke will develop cancer. This (expected) finding does not prove cigarette smoke is not a carcinogen (although the cigarette industry attempted to use the same argument decades ago). This is essentially the argument suggested by Dr. Eaton.
6. While Dr. Eaton suggests the reason Monsanto would not have found cancer in Pre-1970 is due to the fact that not many laboratories were not using Sprague Dawley rats in their cancer study he does not discuss or even broach the more plausible reason not all PCB cancer studies show the same result. And this reason is that Aroclors contained contain varying amounts of a very

toxic and carcinogenic group of impurities or contaminants called polychlorinated dibenzofurans (PCDF). This issue is not discussed by Dr. Eaton but it is a well-known fact among academic and regulatory scientists, governmental agencies and Monsanto scientists. For example, Monsanto's Dr. Levinskas prepared a lengthy (70 page) compendium describing the state-of-the-science discussing PCB toxicity in 1981: *A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls* (MON213337) in which he admits that PCDF were contaminants in Aroclors in his introductory section, stating:

Exhibit 24. Introduction from A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies Biphenyls

INTRODUCTION

This is a review and evaluation of studies which deal with the potential carcinogenicity and mutagenicity of polychlorinated biphenyls (PCBs). It is subdivided into 4 sections: Chronic Rodent Studies, Metabolism Studies, Co-Carcinogenesis Studies and Mutagenicity Studies. A brief summary of Epidemiology Studies is added to complete coverage of the issue of carcinogenicity.

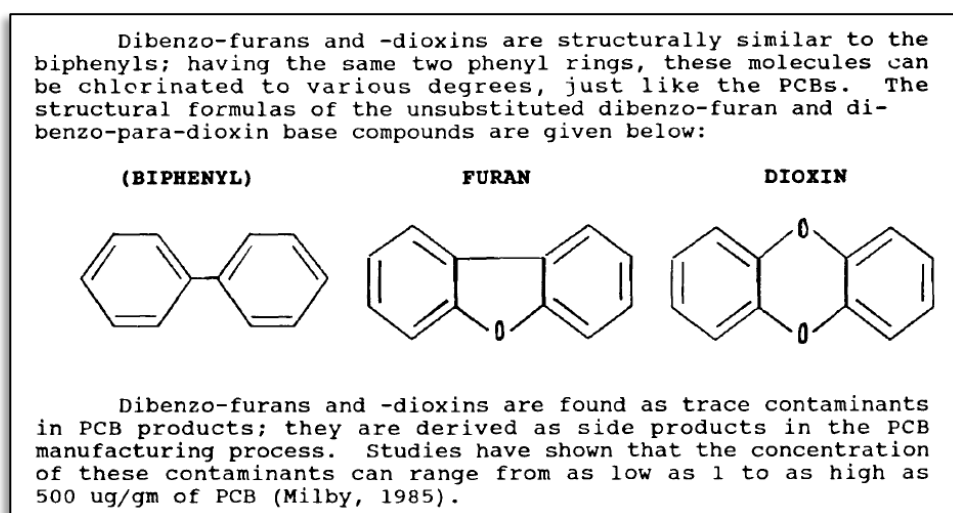
This review does not discuss the effects of impurities or contaminants, particularly polychlorinated dibenzofurans (PCDF), which are reported to be present in some PCB mixtures (Brinkman and deKok, 1980). The presence and amounts of such impurities have not been specified in the materials used in many studies. Thus, attempts to apportion the observed biological effects between impurities and PCBs would only add further conjecture to a subject which currently is rife with speculation.

Source: Levinskas 1981.¹⁷

7. I am also well familiar with this issue because I was a toxicological consultant to the U.S. Department of the Navy, Environmental Health Center, Bureau of Medicine and Surgery for many years investigating PCB polluted Naval Installations sites, conducting toxicological/risk assessments, and training physicians and environmental scientists. As part of my training materials, I used numerous Navy studies and guidance manuals, including:
Polychlorinated Biphenyls (PCBs), *Polychlorinated Dibenzofurans (PCDFs)*,

and Polychlorinated Dioxins (PCDDs) (Navy Environmental Health Center, May 1990),²⁵ to educate the Navy about PCB exposure, risk, and toxicity. This document was well researched and it includes a section on the structural and carcinogenic similarities between PCBs, PCDFs, and PCDDs shown below. It also states that PCDFs have been detected in relative high levels in some PCB batches.

Exhibit 25. Excerpt from Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzofurans (PCDFs), and Polychlorinated Dioxins (PCDDs): Structure of Biphenyl, Furan, and Dioxin



Source: Navy Environmental Health Center 1990.²⁵

8. Because millions of different Aroclor mixtures and batches were produced by Monsanto and each batch of Aroclor contained varying amounts of PCDFs. It is more likely that the varying concentrations of the PCDF contaminants in the various Aroclor mixtures used in different cancer studies contributed to the differences in cancer rates and not the species of rat used by different laboratories in the 1970s and 1980s experiments.

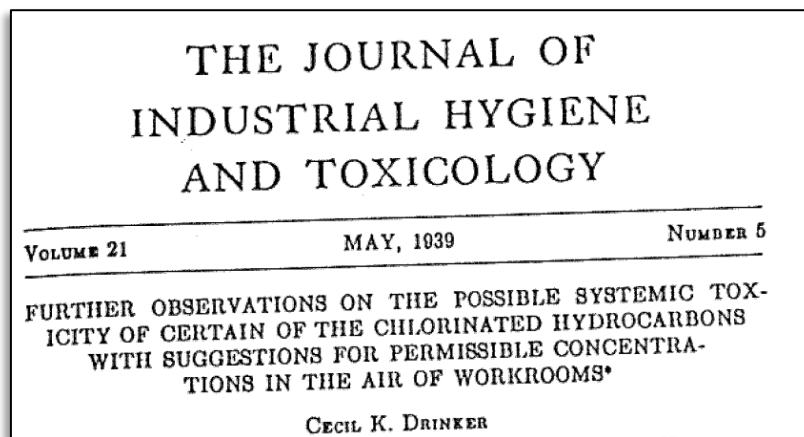
4. SPECIFIC RESPONSES TO DR. EATON'S CRITIQUES- PAGE 96

1. Dr. DeGrandchamp's comparative pathology analysis (beginning on Dr. DeGrandchamp Expert Report, April 5, 2019, p. 39) of Dr. Bennet's tested mixtures is methodologically flawed and scientifically.

My response:

Dr. Eaton misrepresents my opinion and the basis of that opinion. I was aware of the mix-up in the composition of the PCB test mixtures when I reviewed all of the Drinker studies. Dr. Eaton selectively extracted facts I stated in my opinion but failed to consider my entire testimony. My opinion was that adding a small amount (10%) of PCBs to the mixture of penta- and hexachloronaphthalene greatly increased the toxicity of that mixture compared to the mixture of penta- and hexachloronaphthalene without any PCBs. While Dr. Eaton correctly cited the Drinker studies, he omitted the most important part of that study that I discussed in my testimony. The study in question and the one I relied on was the following study:²⁶

Exhibit 26. Cover Page from 1939 Drinker Study



Source: Drinker 1939.²⁶

This is the study that describes the *apparent* mix-up in the chemical composition of the two complex mixtures. What is most important about this study is that it became the sole source of information about the safe exposure levels Dr. Drinker calculated based on his own study results in which he tested the safe exposure levels for 14 different mixtures considering both inhalation and ingestion routes of exposure. Ultimately these suggested permissible levels would become the sole point of reference that industry adopted for worker safety and information about the toxicity of the different mixtures. Dr. Drinkers table is shown below:

Exhibit 27. Table 1 from Drinker 1939: 14 Chlorinated Hydrocarbons, with Chlorine Contents and Permissible Limits for Air in Workrooms

COMPOUND	CHLORINE CONTENT	PERMISSIBLE LIMIT
	%,	mg./cu.m.
1. Trichloronaphthalene plus a trace of tetrachloronaphthalene. Tested upon rats by inhalation and by feeding.....	49.9	10.0
2. Tetra and pentachloronaphthalenes. Tested upon rats by inhalation and by feeding.....	56.4	1.0
3. Penta and hexachloronaphthalenes. Tested upon rats by inhalation and by feeding, and upon dogs by feeding alone.....	62.6	0.5
4. Tetra and pentachloronaphthalenes plus refined chlorinated diphenyl. Tested upon rats by feeding.....	43.5	0.5
5. 90% penta and hexachloronaphthalenes plus 10% chlorinated diphenyl benzene. Tested upon rats by inhalation and by feeding.....	63.0	0.5
6. Chlorinated diphenyl plus chlorinated diphenyl benzene. Tested upon rats by inhalation and by feeding.....	65.0	0.5
7. Chlorinated diphenyl oxide. Tested upon rats by inhalation.....	51.0	0.5
8. Chlorinated diphenyl oxide. Tested upon rats by inhalation.....	57.0	0.5
9. Chlorinated diphenyl. Tested upon rats by inhalation.....	50-55	0.5
10. Hexachlor diphenyl oxide plus 5% trichloronaphthalene. Tested upon rats by inhalation.....	50-55	0.5
11. Hexachloronaphthalene and crude chlorinated diphenyl. Tested upon rats by inhalation.....	Un-known	0.5
12. Special chlorinated naphthalene. Tested upon rats by inhalation.....	50-56	0.5
13. Chlorinated diphenyl. Tested upon rats by inhalation.....	68	10.0
14. Chlorinated diphenyl benzene. Tested upon rats by inhalation.....	60	0.5

* The analytical method and apparatus used routinely for field determinations is that described by Tebbens (Toxic J., 19, 204 (1937)) and by Drinker et al. (ibid., p. 283).

Source: Drinker 1939.²⁶

This table shows that for Mixture 2, which only contains tetra and pentachloronaphthalene the permissible level is 1.0 milligram/cubic meter. However, when refined PCB was added to that mixture (tetra and pentachloronaphthalene) the toxicity was *twice* as great as the Mixture of tetra and pentachloronaphthalene alone as the permissible exposure level was cut in half at: 0.5 milligram/cubic meter. Dr. Eaton failed to present or even discuss this table and these facts in his opinion.

Dr. Eaton's opinion that Mixture 2 *also* contained chlorinated diphenyl benzene is not supported by this *final* table of permissible levels that *all* PCB customers adopted as the "standard permissible" exposure levels of PCBs and chlorinated naphthalenes. If Dr. Eaton's opinion is correct then Dr. Drinker would have described Mixture 2 as containing tetra and pentachloronaphthalene and refined PCB *plus* chlorinated diphenyl benzene. The table does not state this fact. The table supports my opinion that Mixture 2 only contained the chlorinated naphthalene and PCBs.

It is conventional and generally accepted practices when scientists find an error in their published studies to issue an *erratum* to correct any errors. This is particularly true when the mistake could have grave consequences like publishing the permissible levels of exposure that are used as the sole metric to protect workers. I am not aware of any future publication that the Drinker team published any errata for any of the Drinker series of studies. They would also have issued an erratum for the earlier histopathological studies in which they state chlorinated diphenyl was the most toxic of all the compounds they tested:

Of the various chlorinated hydrocarbons tested, chlorinated diphenyl gave evidence of being the most toxic.

This final definitive and clear conclusion that was stated in the Drinker study (Bennett et al. 1938) has never been retracted or modified or changed since this conclusion was reached.

Dr. Eaton also ignores the additional supporting facts from my testimony. I stated that my opinion that PCBs were extremely toxic and produced severe histopathologic lesions that were in fact identical to those reported by Dr. Miller of the Public Health Service (Miller, 1944) which were hyaline bodies. In fact, hyaline bodies were by far the most important morphological

damage he discussed. The most important fact from the Miller study was that there can be no dispute that PCBs *caused* these pathological lesions because animals were only exposed to PCBs were used in his study, a fact which Dr. Eaton failed to acknowledge or discuss. Indeed, he went on to stress that he was not only testing PCBs but that he was testing the “commercial” grade, which is the same formulation that Monsanto was selling to their customers (as opposed to a pure grade):

Only the pathologic changes in animals exposed to a commercial chlorinated diphenyl are given here.

He stressed the fact that he is “only” reporting PCB-induced lesion because he was aware of the Drinker studies in which mixtures of PCBs and chlorinated naphthalenes were tested. His stated conclusion is consistent with mine as he references the same histopathological lesions that were reported in the Drinker studies. In comparing the Drinker study findings to his own, he came to the same conclusion I stated in my opinion. In fact, he stated the identical opinion about hyaline bodies lesions being greater in PCB-treated animals compared to chlorinated naphthalene. Based on his review of the Drinker studies and a comparison to his pathological findings of the hyaline lesions, he made the following conclusion:

The intracellular hyaline bodies were found in the rat liver alone...These findings agree with Bennett who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.

Miller’s statement is identical to mine, which I stated in my testimony.

2. Dr. DeGrandchamp misrepresents that mitotic bodies and hyaline bodies were markers for early hallmark of tumorigenesis at the time of the Drinker and Bennet studies in the 1930s.

My response:

Dr. Eaton misstates my opinion. I stated that mitotic figures and hyaline bodies *should have* been a trigger for Monsanto to conduct long-term cancer studies for PCBs. These two specific pathological lesions were established histopathological criteria identified and discussed in numerous historical studies I discussed in my report starting with the early 1900s. By the 1930s and 1940s they were key pathological criteria.

I did not state the appearance of mitotic figures and hyaline bodies were in fact *evidence that a tumor would develop* in the PCB-treated animals, because it would be impossible to make that prediction because the animals were killed at ~3 months. The final determination of the eventual outcome of those lesions is unknown and speculative. As I stated, the Drinker and Miller studies were subacute studies—not cancer studies. My opinion is that the appearance of those highly unusual pathological lesions that were described in the Drinker and Miller studies should have been a “trigger” or red flag as they were known to be lesions that were well-described in *other* (non-PCB) cancer studies. That is, I am posing the question of what would have been the eventual outcome of those highly damage rat livers if they were exposed to PCB in an actual chronic lifetime cancer study—should the uniqueness and severity of the lesions prompted an independent competent scientist to have concluded that it would be a good idea to start a long-term animal cancer study. Dr. Eaton holds a different opinion, seeming to conclude the pathology was seen in all types of liver damage. He therefore does not agree that the PCB lesions were important and that he would not have continued further toxicological investigations.

Dr. Eaton does not discuss the conclusions of Drinker and Miller with regard to both the severity and *uniqueness* of the hyaline bodies. Scientist typically choose the words they use to describe pathological features very carefully. Anytime a pathological description includes the term “peculiar” or unique it typically focuses the attention of other scientist reviewing their findings. This is how Drinker described the “peculiar” hyaline bodies:

Feeding of tetra- and pentachloronaphthalenes in combination with chlorinated diphenyl resulted in pronounced liver changes. These livers had increased in weight (average 71 per cent). Microscopic examination revealed a peculiar type of hyaline degeneration involving practically every liver cell (see figs. 1 and 2, plate I). This type of cell degeneration was more marked and occurred earlier after exposure to preparations containing chlorinated diphenyl than to any other compounds tested. Furthermore, it was most marked in the livers of animals exposed to refined chlorinated diphenyl (figs. 4, 5, and 6, plate III).

Miller also focused on the presence of hyaline bodies in his PCB study far more than any other pathological feature and a photomicrograph of hyaline bodies was the *only one* he presented in his study.

Although, it is impossible to definitively conclude whether the PCB-induced lesions would have been repaired as Dr. Eaton's opinion suggests or whether the lesions would have developed into a carcinogenic response because the animals were killed too early. Neither of us can be certain- but I was not making a prediction. I was simply stating that since the lesions were "peculiar" or unusual and there were significant mitotic figures it was more likely that the liver would have proceeded to show true carcinogenic effects. Obviously, in retrospect my opinion is more likely since PCBs have been shown to precede along the same tumorigenic path when chronic animal testing was eventually carried out in the 1970s.

The one fact that Dr. Eaton ignores-or at least does not discuss in his report-which is the most important finding in the Drinker studies is that they stopped PCB dosing and the rats were allowed to recover from the liver damage; the livers did not recover and the damage was still the same. This evidence is contradictory to Dr. Eaton's opinion that the pathological lesions described by Drinker were simply the normal changes that occur during regeneration and repair from PCB-induced damage. Obviously, the damage was not due to repair processes. This apparently important enough to Drinker to run the study and report his findings.

In these instances the hyalin degeneration of the cell cytoplasm was more marked. Although rats inhaling low concentrations of compounds D and F showed no demonstrable signs of ill health, microscopic examination of their livers revealed marked liver cell injury (fig. 6, plate II, and fig. 3, plate III). These lesions were still demonstrable after a 2 months' recovery period.

I also did not state that mitotic figures and hyaline bodies are *only* seen in cancerous tissue. I stated that it is possible that the histopathology could be due to regeneration-but as stated about was unlikely.

Finally, it is not clear if Dr. Eaton is suggesting that mitotic figures *are not* evidence of tumors. If this is the case, I disagree because tumor formation cannot occur without cell division. In fact, that is the very definition of a tumor-uncontrolled cell division. Mitotic figures are simply visual microscopic evidence of dividing cells. In the clinical setting, mitotic figures are perhaps the most important histological criteria that are used for tumor diagnoses, tumor staging, and tumor prognoses.

Lastly, I considered Dr. Millers finding that the hyaline bodies were not examples of pathologic changes. He specifically that hyaline bodies *were not seen* before 50 days of exposure indicating they are more likely part of the carcinogenic sequelae rather than simple pathological lesions. If they were simple pathological lesions they would certainly be observed early in the pathological response-rather than only suddenly appearing after ~2 months of exposure which he states below:

Intracellular hyaline bodies were found in the liver of the rat alone. They were present, usually in large numbers, in all of the rats receiving 10 0.05-cc. doses and in some of the animals receiving 25 doses by skin and corneal applications and ingestion, but were not observed in any of the animals subjected to single doses. These bodies were noted in the animals sacrificed 50, 60, and 90 days after first exposure. None were observed in rats examined prior to 50 days on test. They occurred in from 20 to 38 percent of the animals treated in the various ways. They were somewhat less marked in degree and in number of animals when the chlorinated diphenyl was ingested. These findings agree with Bennett (7) who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.

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